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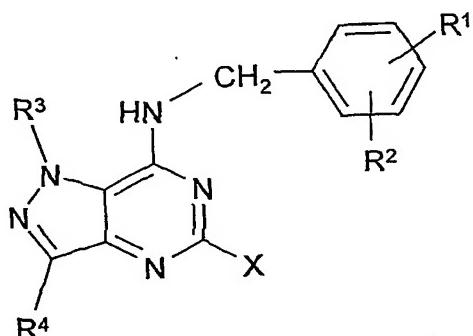
**WO 02/062343 A2**

(54) Title: PHARMACEUTICAL FORMULATION COMPRISING PYRAZOLO[4,3-d]PYRIMIDINES AND ENDOTHELIN RECEPTOR ANTAGONISTS OR THIENOPYRIMIDINES AND ENDOTHELIN RECEPTOR ANTAGONISTS

(57) Abstract: Pharmaceutical preparation comprising at least one phosphodiesterase V inhibitor have, and/or physiologically acceptable salts and/or solvates thereof and at least one endothelin receptor antagonist for the preparation of a medicament for the treatment of angina, high blood pressure, high pulmonary pressure, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cor pulmonale, dextrocardiac insufficiency, atherosclerosis, conditions of reduced patency of the heart vessels, peripheral vascular diseases, strokes, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, irritable bowel syndrome, tumours, renal insufficiency, liver cirrhosis, erectile dysfunction and for the treatment of female sexual disorders.

**Pharmaceutical formulation comprising
pyrazolo[4,3-d]pyrimidines and endothelin receptor antagonists
or thienopyrimidines and endothelin receptor antagonists**

- 5 The invention relates to pharmaceutical formulations comprising at least one phosphodiesterase V inhibitor and/or physiologically acceptable salts and/or solvates thereof and at least one endothelin receptor antagonist.
- 10 The invention relates in particular to pharmaceutical formulations comprising at least one compound of the formula I



- 20 in which
R¹ and R² are each, independently of one another, H, A, OH, OA or Hal,
R¹ and R² together are alternatively alkylene having 3-5 carbon atoms, -O-CH₂-CH₂-, -CH₂-O-CH₂-, -O-CH₂-O- or -O-CH₂-CH₂-O-,
- 25 R³ and R⁴ are each, independently of one another, H or A,
X is R⁵, R⁶ or R⁷, each of which is monosubstituted by R⁸,
R⁵ is linear or branched alkylene having 1-10 carbon atoms, in which one or two CH₂ groups may be replaced by -CH=CH- groups, O, S or SO,
30 R⁶ is cycloalkyl or cycloalkylalkylene having 5-12 carbon atoms,
R⁷ is phenyl or phenylmethyl,
R⁸ is COOH, COOA, CONH₂, CONHA, CON(A)₂ or CN,
35 A is alkyl having from 1 to 6 carbon atoms, and
Hal is F, Cl, Br or I,

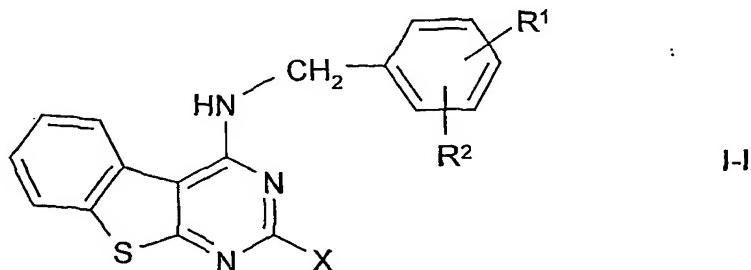
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and/or physiologically acceptable salts and/or solvates thereof and at least one endothelin receptor antagonist.

5 The invention furthermore relates to pharmaceutical formulations comprising at least one phosphodiesterase V inhibitor and/or physiologically acceptable salts and/or solvates thereof and at least one endothelin receptor antagonist.

10 The invention relates in particular to pharmaceutical formulations comprising at least one compound of the formula I-I

15



in which

- 20 R¹ and R² are each, independently of one another, H, A, OA, OH or Hal,
- 25 R¹ and R² together are alternatively alkylene having 3-5 carbon atoms, -O-CH₂-CH₂-, -CH₂-O-CH₂-, -O-CH₂-O- or -O-CH₂-CH₂-O-,
- 30 X is R⁴, R⁵ or R⁶, each of which is monosubstituted by R⁷, R⁴ is linear or branched alkylene having 1-10 carbon atoms, in which one or two CH₂ groups may be replaced by -CH=CH- groups,
- R⁵ is cycloalkyl or cycloalkylalkylene having 5-12 carbon atoms,
- R⁶ is phenyl or phenylmethyl,
- R⁷ is COOH, COOA, CONH₂, CONHA, CON(A)₂ or CN,
- A is alkyl having from 1 to 6 carbon atoms, and
- Hal is F, Cl, Br or I,
- 35 and/or physiologically acceptable salts and/or solvates thereof and at least one endothelin receptor antagonist.

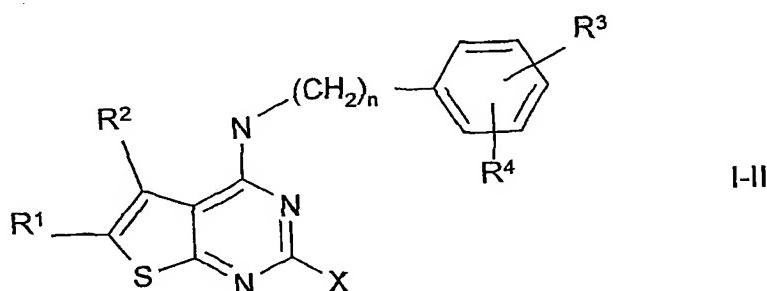
- 3 -

The invention furthermore relates to pharmaceutical formulations comprising at least one phosphodiesterase V inhibitor and/or physiologically acceptable salts and/or solvates thereof and at least one endothelin receptor antagonist.

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The invention relates in particular to pharmaceutical formulations comprising at least one compound of the formula I-II

10



15

in which

R¹ and R² are each, independently of one another, H, A or Hal, where one of the radicals R¹ or R² is always ≠ H,

20

R¹ and R² together are alternatively alkylene having 3-5 carbon atoms,

R³ and R⁴ are each, independently of one another, H, A, OH, OA or Hal,

R³ and R⁴ together are alternatively alkylene having 3-5 carbon atoms, -O-CH₂-CH₂-, -O-CH₂-O- or -O-CH₂-CH₂-O-,

25

X is R⁵ or R⁶, each of which is monosubstituted by R⁷,

R⁵ is linear or branched alkylene having 1-10 carbon atoms, in which one or two CH₂ groups may be replaced by -CH=CH-groups, or -C₆H₄-(CH₂)_m-,

30

R⁶ is cycloalkylalkylene having 6-12 carbon atoms,

R⁷ is COOH, COOA, CONH₂, CONHA, CON(A)₂ or CN,

A is alkyl having from 1 to 6 carbon atoms,

Hal is F, Cl, Br or I,

m is 1 or 2, and

35

n is 0, 1, 2 or 3,

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and/or physiologically acceptable salts and/or solvates thereof and at least one endothelin receptor antagonist.

The invention furthermore relates to the use of the formulation for the
5 preparation of a medicament for the treatment of angina, high blood
pressure, high pulmonary pressure, congestive heart failure (CHF), chronic
obstructive pulmonary disease (COPD), cor pulmonale, dextrocardiac
insufficiency, atherosclerosis, conditions of reduced patency of the heart
vessels, peripheral vascular diseases, strokes, bronchitis, allergic asthma,
10 chronic asthma, allergic rhinitis, glaucoma, irritable bowel syndrome,
tumours, renal insufficiency, liver cirrhosis, erectile dysfunction and for the
treatment of female sexual disorders.

15 Pharmaceutical formulations consisting of other phosphodiesterase V
(PDE V) inhibitors together with a second active ingredient are described
in WO 00/15639. Combinations of PDE V inhibitors with endothelin
receptor antagonists are also described, for example, in WO 99/64004.

20 The use of other PDE V inhibitors is described, for example, in WO
94/28902.

The invention was based on the object of providing novel medicaments in
the form of pharmaceutical preparations which have better properties than
known medicaments which can be used for the same purpose.

25 This object has been achieved by the discovery of the novel preparation.

30 The compounds of the formulae I, I-I and I-II and their salts have very
valuable pharmacological properties and are well tolerated.
In particular, they exhibit specific inhibition of cGMP phosphodiesterase
(PDE V).

35 Quinazolines having a cGMP phosphodiesterase-inhibiting activity are
described, for example, in J. Med. Chem. 36, 3765 (1993) and ibid. 37,
2106 (1994).

- The biological activity of the compounds of the formulae I, I-I and I-II can be determined by methods as described, for example, in WO 93/06104. The affinity of the compounds according to the invention for cGMP and cAMP phosphodiesterase is determined by measuring their IC₅₀ values (concentration of the inhibitor needed to achieve 50% inhibition of the enzyme activity).
- 5 The determinations can be carried out using enzymes isolated by known methods (for example W.J. Thompson et al., Biochem. 1971, 10, 311). The experiments can be carried out using a modified batch method of W.J.
- 10 Thompson and M.M. Appleman (Biochem. 1979, 18, 5228).
- The compounds are therefore suitable for the treatment of illnesses of the cardiovascular system, in particular cardiac insufficiency, and for the treatment and/or therapy of potency disorders (erectile dysfunction).
- 15 The use of substituted pyrazolopyrimidinones for the treatment of impotence is described, for example, in WO 94/28902.
- The compounds are effective as inhibitors of phenylephrine-induced contractions in corpus cavernosum preparations of rabbits. This biological action can be demonstrated, for example, by the method described by F. Holmquist et al. in J. Urol., 150, 1310-1315 (1993).
- 20 The inhibition of the contraction demonstrates the effectiveness of the compounds according to the invention for the therapy and/or treatment of potency disorders.
- 25 The efficacy of the pharmaceutical formulations according to the invention, in particular for the treatment of high pulmonary pressure, can be demonstrated as described by E. Braunwald in Heart Disease 5th edition, WB Saunders Company, 1997, chapter 6: Cardiac catheterisation 177-200.
- 30 The compounds of the formulae I, I-I and I-II can be employed as medicament active ingredients in human and veterinary medicine. They can furthermore be employed as intermediates for the preparation of further medicament active ingredients.
- 35

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Compounds of the formula I

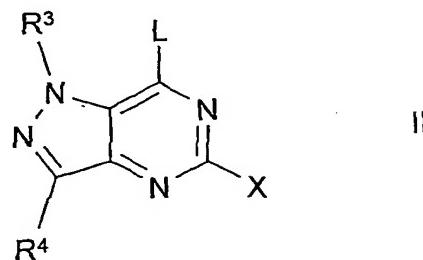
The compounds of the formula I according to Claim 1 and their salts are prepared by a process

5

characterised in that

- a) a compound of the formula II

10



15

in which

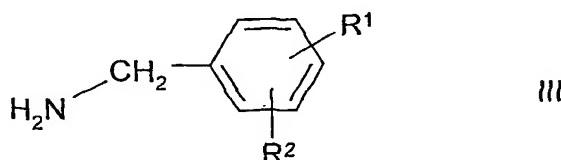
R³, R⁴ and X are as defined above,

20

and L is Cl, Br, OH, SCH₃ or a reactive esterified OH group,

is reacted with a compound of the formula III

25



in which

30

R¹ and R² are as defined above,

or

35

- b) a radical X in a compound of the formula I is converted into another radical X by, for example, hydrolysing an ester group to a COOH group or converting a COOH group into an amide or into a cyano group,

and/or in that a compound of the formula I is converted into one of its salts.

The term solvates of the compounds of the formula I is taken to mean
adducts of inert solvent molecules onto the compounds of the formula I
which form owing to their mutual attractive force. Solvates are, for
example, mono- or dihydrates or alcoholates.

Above and below, the radicals R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, X and L have
the meanings indicated for the formulae I, II and III, unless expressly
stated otherwise.

A is alkyl having 1-6 carbon atoms.

In the above formulae, alkyl is preferably unbranched and has 1, 2, 3, 4, 5
or 6 carbon atoms and is preferably methyl, ethyl or propyl, furthermore
preferably isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, but also
n-pentyl, neopentyl, isopentyl or hexyl.

X is an R⁵, R⁶ or R⁷ radical which is monosubstituted by R⁸.

R⁵ is a linear or branched alkylene radical having 1-10 carbon atoms,
where the alkylene radical is preferably, for example, methylene, ethylene,
propylene, isopropylene, butylene, isobutylene, sec-butylene, pentylene, 1-
, 2- or 3-methylbutylene, 1,1-, 1,2- or 2,2-dimethylpropylene, 1-ethylpropyl-
ene, hexylene, 1-, 2-, 3- or 4-methylpentylene, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or
3,3-dimethylbutylene, 1- or 2-ethylbutylene, 1-ethyl-1-methylpropylene, 1-
ethyl-2-methylpropylene, 1,1,2- or 1,2,2-trimethylpropylene, linear or
branched heptylene, octylene, nonylene or decylene.

R⁵ is furthermore, for example, but-2-enylene or hex-3-enylene.

One CH₂ group in R⁵ may preferably be replaced by oxygen.

Very particular preference is given to ethylene, propylene, butylene or CH₂-
O-CH₂.

R⁶ is cycloalkylalkylene having 5-12 carbon atoms, preferably, for example,
cyclopentylmethylen, cyclohexylmethylen, cyclohexylethylen,
cyclohexylpropylene or cyclohexylbutylene.

R^6 is alternatively cycloalkyl, preferably having 5-7 carbon atoms. Cycloalkyl is, for example, cyclopentyl, cyclohexyl or cycloheptyl.

Hal is preferably F, Cl or Br, but alternatively I.

5

The radicals R^1 and R^2 may be identical or different and are preferably in the 3- or 4-position of the phenyl ring. They are, for example, each, independently of one another, H, alkyl, OH, F, Cl, Br or I or together are alkylene, such as, for example, propylene, butylene or pentylene, furthermore more ethyleneoxy, methylenedioxy or ethylenedioxy. They are alternatively preferably each alkoxy, such as, for example, methoxy, ethoxy or propoxy.

10

15 The radical R^8 is preferably, for example, COOH, COOA, such as, for example, COOCH_3 or COOC_2H_5 , CONH_2 , $\text{CON}(\text{CH}_3)_2$, CONHCH_3 or CN, but in particular COOH or COOA.

Throughout the invention, all radicals which occur more than once may be identical or different, i.e. are independent of one another.

20

The invention relates, in particular, to pharmaceutical formulations comprising an endothelin receptor antagonist and at least one compound of the formula I in which at least one of the said radicals has one of the preferred meanings indicated above. Some preferred groups of compounds may be expressed by the following sub-formulae Ia to If, which conform to the formula I and in which the radicals not designated in greater detail have the meaning indicated for the formula I, but in which

25

in Ia X is R^5 , phenyl or phenylmethyl, each of which is substituted by COOH, COOA, CONH_2 , CONA_2 , CONHA or CN;

30

in Ib R^1 and R^2 together are alkylene having 3-5 carbon atoms, $-\text{O}-\text{CH}_2-\text{CH}_2-$, $-\text{O}-\text{CH}_2-\text{O}-$ or $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$,
X is R^5 , phenyl or phenylmethyl, each of which is substituted by COOH, COOA, CONH_2 , CONA_2 , CONHA or CN;

35

	in Ic	R ¹ and R ²	are each, independently of one another, H, A, OH, OA or Hal,
5		R ¹ and R ²	together are alternatively alkylene having 3-5 carbon atoms, -O-CH ₂ -CH ₂ -, -O-CH ₂ -O- or -O-CH ₂ -CH ₂ -O-,
	X		is R ⁵ , phenyl or phenylmethyl, each of which is substituted by COOH, COOA, CONH ₂ , CONA ₂ , CONHA or CN;
10	in Id	R ¹ and R ²	are each, independently of one another, H, A, OH, OA or Hal,
	R ¹ and R ²		together are alternatively alkylene having 3-5 carbon atoms, -O-CH ₂ -CH ₂ -, -O-CH ₂ -O- or -O-CH ₂ -CH ₂ -O-,
15	X		is alkylene having 2-5 carbon atoms, cyclohexyl, phenyl or phenylmethyl, each of which is monosubstituted by R ⁸ ,
	R ³		is alkyl having 1-6 carbon atoms,
	R ⁴		is alkyl having 1-6 carbon atoms,
	R ⁸		is COOH or COOA,
20	A		is alkyl having from 1 to 6 carbon atoms,
	Hal		is F, Cl, Br or I;
	in Ie	R ¹ and R ²	are each, independently of one another, H, A, OH, OA or Hal,
25		R ¹ and R ²	together are alternatively alkylene having 3-5 carbon atoms, -O-CH ₂ -CH ₂ -, -O-CH ₂ -O- or -O-CH ₂ -CH ₂ -O-,
	R ³		is alkyl having 1-6 carbon atoms,
	R ⁴		is alkyl having 1-6 carbon atoms,
30	X		is -(CH ₂) ₂₋₅ -R ⁸ , 4-R ⁸ -cyclohexyl, 4-R ⁸ -phenyl or 4-(R ⁸ -methyl)phenyl;
	in If	R ¹ and R ²	are each, independently of one another, H, A, OH, OA or Hal,
35		R ¹ and R ²	together are alternatively alkylene having 3-5 carbon atoms, -O-CH ₂ -CH ₂ -, -O-CH ₂ -O- or -O-CH ₂ -CH ₂ -O-,
	R ³		is alkyl having 1-6 carbon atoms,

- 10 -

	R^4	is alkyl having 1-6 carbon atoms,
	X	is $-(CH_2)_{2-5}R^8$, in which one CH_2 group may be replaced by O, or is 4- R^8 -cyclohexyl, 4- R^8 -phenyl or 4-(R^8 -methyl)phenyl,
5	R^8	is COOH or COOA.

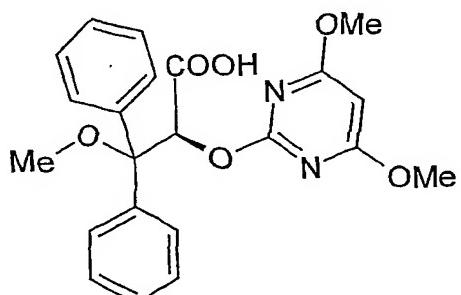
The invention preferably relates to a formulation comprising [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl-methoxy]acetic acid and physiologically acceptable salts and/or solvates thereof and an endothelin receptor antagonist.
10 Besides the free acid, the ethanolamine salt is preferred.

Preferred endothelin receptor antagonists are bosentan, tezosentan and sitaxentan (TBC-11251; J.Med.Chem., 40, No.11, 1690-97, 1997).
15 Preferred endothelin receptor antagonists are thus furthermore
a) BMS-193884 (EP 558258),
b) BMS-207940 (Pharmaprojects (13.06.97)),
c) BQ-123 (Exp.Opin.Invest.Drugs, 1997, 6, No.5, 475-487),
d) SB-209670 (Exp.Opin.Invest.Drugs, 1997, 6, No.5, 475-487),
20 e) SB-217242 (Exp.Opin.Invest.Drugs, 1997, 6, No.5, 475-487),
f) SB-209598 (Trends in Pharmacol. Sci., 17, 177-81, 1996),
g) TAK-044 (Exp.Opin.Invest.Drugs, 1997, 6, No.5, 475-487),
h) Bosentan (Trends in Pharmacol. Sci., 18, 408-12, 1997),
i) PD-156707 (J.Med.Chem., 40, No.7, 1063-74, 1997),
25 j) L-749329 (Bioorg.Med.Chem.Lett., 7, No.3, 275-280, 1997),
k) L-754142 (Exp.Opin.Invest.Drugs, 1997, 6, No.5, 475-487),
l) ABT-627 (J.Med.Chem., 40, No.20, 3217-27, 1997),
m) A-127772 (J.Med.Chem., 39, No.5, 1039-1048, 1996),
n) A-206377 (213th American Chemical Society National Meeting, San
30 Francisco, California, USA, 13 – 17 April 1997, Poster, MEDI 193),
o) A-182086 (J.Med.Chem., 40, No.20, 3217-27, 1997),
p) EMD-93246 (211th American Chemical Society National Meeting,
New Orleans, USA, 1996, Poster, MEDI 143),
q) EMD-122801 (Bioorg.Med.Chem.Lett., 8, No.1, 17-22, 1998),
35 r) ZD-1611 (Trends in Pharmacol. Sci., 18, 408-12, 1997),
s) AC-610612 (R&D Focus Drug News (18.05.98)),

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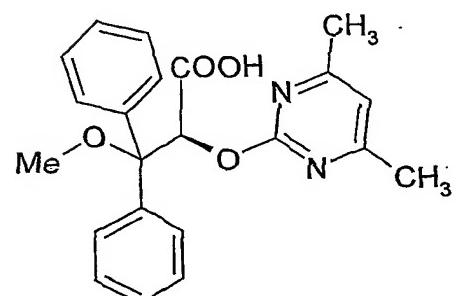
- t) T-0201 (70th Annual Meeting of the Japanese Pharmacological Society, Chiba, Japan, 22-15 March 1997, Lecture, O-133),
u) J-104132 (R&D Focus Drug News (15.12.97)),

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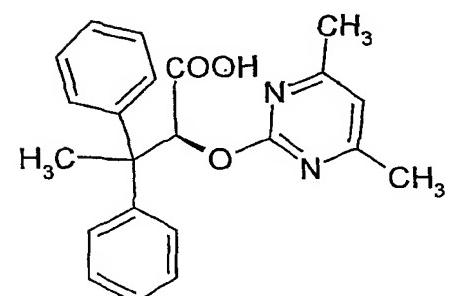
v)



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w)

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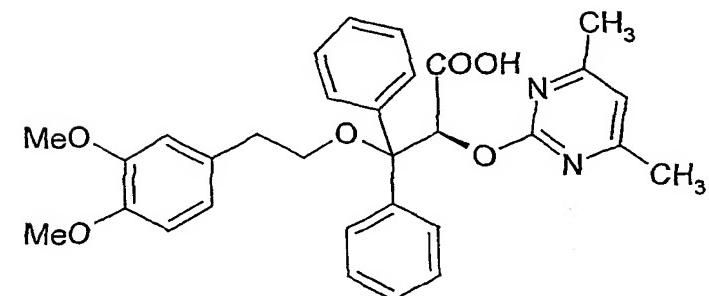
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x)

30

35

y)

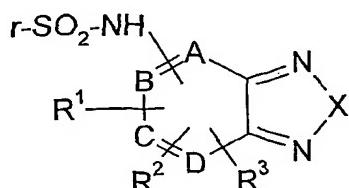


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Particularly preferred endothelin receptor antagonists are, for example,

a) the compounds of the formula I described in EP 0733626

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I

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in which

-A=B-C=D- is a -CH=CH-CH=CH- group in which 1 or 2 CH has (have) been replaced by N,

15

Ar is Ph or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by H, Hal, A, alkenyl having up to 6 carbon atoms, Ph, OPh, NO₂, NR⁴R⁵, NHCOR⁴, CF₃, OCF₃, CN, OR⁴, COOR⁴, (CH₂)_nCOOR⁴, (CH₂)_nNR⁴R⁵, -N=C=O or NHCONR⁴R⁵,

20

R¹, R² and R³ are each, independently of one another, absent, H, Hal, A, CF₃, NO₂, NR⁴R⁵, CN, COOR⁴, NHCOR⁴,

R⁴ and R⁵ are each, independently of one another, H or A, or together are alternatively -CH₂-(CH₂)_n-CH₂-,

25

A is alkyl having from 1 to 6 carbon atoms,

Ph is phenyl,

X is O or S,

Hal is F, Cl, Br or I,

n is 1, 2 or 3,

30

and their salts, with the exception of

4-methyl-N-(2,1,3-benzothiadiazol-4-yl)benzenesulfonamide,

4-methyl-N-(2,1,3-benzothiadiazol-5-yl)benzenesulfonamide, 4-nitro-

N-(2,1,3-benzothiadiazol-4-yl)benzenesulfonamide, 4-nitro-N-(2,1,3-

benzothiadiazol-5-yl)benzenesulfonamide, 4-amino-N-(2,1,3-benzo-

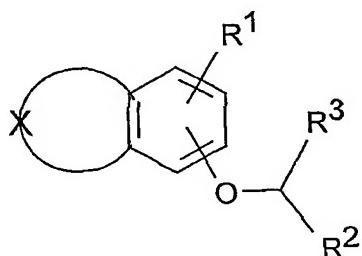
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thiadiazol-4-yl)benzenesulfonamide and 4-amino-N-(2,1,3-benzothiadiazol-5-yl)benzenesulfonamide;

- 13 -

b) the compounds of the formula I described in EP 0733626

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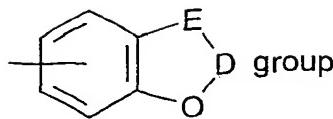


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in which

- X is a saturated, partially unsaturated or completely unsaturated 3- to 4-membered alkylene chain, in which from 1 to 3 carbon atoms may be replaced by N and/or from 1 to 2 carbon atoms may be replaced by 1-2 O atoms and/or 1-2 S atoms, but where at most up to 3 carbon atoms may be replaced and where, in addition, a single, double or triple substitution of the alkylene chain and/or of a nitrogen located therein by A, R⁸ and/or NR⁴R⁴ may occur, and where furthermore one CH₂ group in the alkylene chain may also be replaced by a C=O group,
- A is alkyl having 1-6 carbon atoms, in which one or two CH₂ groups may be replaced by O or S atoms or by -CR⁴=CR⁴- groups and in addition 1-7 H atoms may be replaced by F,
- R¹ is H or A,
- R² is COOR⁴, CN, 1H-tetrazol-5-yl or CONHSO₂R⁸,
- R³ is Ar,
- 30 R⁴ and R^{4'} are each, independently of one another, H, alkyl having from 1 to 6 carbon atoms or benzyl,
- Ar is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R⁵, R⁶ or R⁷, or is a

35



5 which is unsubstituted or monosubstituted or disubstituted in the phenyl part by R^5 or R^6 ,

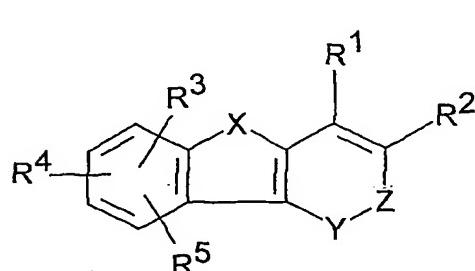
10 R^5 , R^6
 and R^7 are each, independently of one another, R^4 , OR^4 , Hal,
 CF_3 , OCF_3 , OCH_2F , OCH_2Cl , NO_2 , NR^4R^4 , $NHCOR^4$,
 CN , $NHSO_2R^4$, $COOR^4$, COR^4 , $CONHSO_2R^8$, $O(CH_2)_nR^2$,
 OPh , $O(CH_2)_nOR^4$ or $S(O)_mR^4$,

R^8 is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR¹, NR²R⁴ or Hal,

15 E is CH_2 or O,
 D is carbonyl or $[\text{C}(\text{R}^4\text{R}^4')_n]$,
 Hal is F, Cl, Br or I,
 m is 0, 1 or 2,
 n is 1 or 2,

 20 and their salts:

→ all the compounds of the formula I described in EP 0755934



30

in which

-Y-Z- is $-\text{NR}^7\text{-CO-}$, $-\text{N=C(OR}^7\text{)-}$ or $-\text{N=CR}^8\text{-}$,

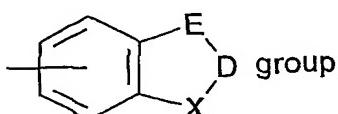
R^1 is Ar.

R^2 is COOR^6 , CN , 1H-tetrazol-5-yl or CONHSO_2Ar ,

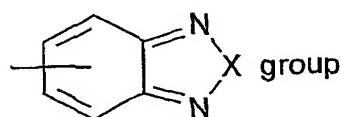
35 R³ R⁴

- 15 -

and R ⁵	are each, independently of one another, R ⁶ , OR ⁶ , S(O) _m R ⁶ , Hal, NO ₂ , NR ⁶ R ⁶ , NHCOR ⁶ , NHSO ₂ R ⁶ , OCOR ⁶ , COOR ⁶ or CN,
R ⁶ and R ⁶	are each, independently of one another, H, alkyl having from 1 to 6 carbon atoms, benzyl or phenyl,
R ⁷	is (CH ₂) _n Ar,
R ⁸	is Ar or OAr,
Ar	is phenyl which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R ⁹ , R ¹⁰ or R ¹¹ , or is unsubstituted naphthyl or a



15 which is unsubstituted or monosubstituted or disubstituted in the phenyl part by R^9 or R^{10} , or is a



which is unsubstituted or monosubstituted or disubstituted in the cyclohexadienyl part by R⁹ or R¹⁰,

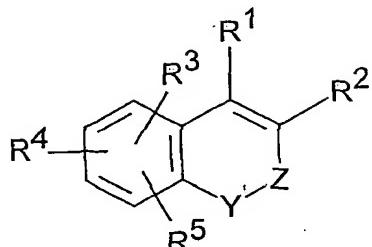
R^9, R^{10}
and R^{11} are each, independently of one another, R^6 , OR^6 , Hal,
 CF_3 , OCF_3 , $OCHF_2$, OCH_2F , NO_2 , NR^6R^6' , $NHCOR^6$, CN,
 $NHSO_2R^6$, $COOR^6$, COR^6 , $CONHSO_2Ar$, $O(CH_2)_nR^2$,
 $O(CH_2)_nOR^6$ or $S(O)_mR^6$,

E	is CH ₂ , S or O,
D	is carbonyl or [C(R ⁶ R ^{6'})] _n ,
Hal	is F, Cl, Br or I,
X	is O or S,
m	is 0, 1 or 2,
n	is 1 or 2,

and their salts;

d) the compounds of the formula I described in EP 0757039

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in which

-Y-Z- is $-\text{NR}^7\text{-CO-}$, $-\text{N=C(OR}^7\text{)-}$ or $-\text{N=CR}^8\text{-}$,

R¹ is Ar,

R² is COOR⁶, $(\text{CH}_2)_n\text{COOR}^6$, CN, 1H-tetrazol-5-yl or CONHSO₂Ar,

15

R³, R⁴ and R⁵ are each, independently of one another, R⁶, OR⁶, S(O)_mR⁶, Hal, NO₂, NR⁶R⁶, NHCOR⁶, NHSO₂R⁶, OCOR⁶, COR⁶, COOR⁶ or CN, where R³ and R⁴ together may alternatively be an O(CH₂)_nO group,

20

R⁶ and R⁶' are each, independently of one another, H, alkyl having from 1 to 6 carbon atoms, benzyl or phenyl,

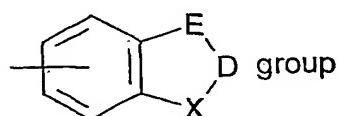
R⁷ is (CH₂)_nAr,

R⁸ is Ar or OAr,

25

Ar is phenyl which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R⁹, R¹⁰ or R¹¹, or is unsubstituted naphthyl or a

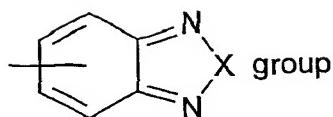
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35

which is unsubstituted or monosubstituted or disubstituted in the phenyl part by R⁹ or R¹⁰, or is a

- 17 -



5

which is unsubstituted or monosubstituted or disubstituted in the cyclohexadienyl part by R⁹ or R¹⁰,

R⁹, R¹⁰and R¹¹

are each, independently of one another, R⁶, OR⁶, Hal, CF₃, OCF₃, OCHF₂, OCH₂F, NO₂, NR⁶R^{6'}, NHCOR⁶, CN, NHSO₂R⁶, COOR⁶, COR⁶, CONHSO₂Ar, O(CH₂)_nR²,

O(CH₂)_nOR⁶ or S(O)_mR⁶,E is CH₂, S or O,D is carbonyl or [C(R⁶R^{6'})]_n,

X is O or S,

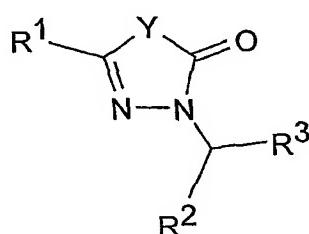
15 Hal is F, Cl, Br or I,

m is 0, 1 or 2,

n is 1 or 2,

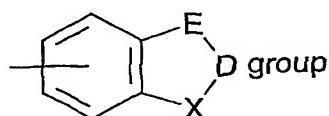
and their salts;

20 e) the compounds of the formula I described in EP 0796250



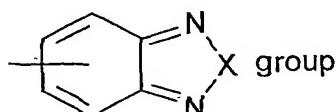
25

in which

Y is -C(R⁴R^{4'})-C(R⁴R^{4'})-, -CR⁴=CR^{4'}- or -C(R⁴R^{4'})-S-,30 R¹ is Het, Ar, R³ or R⁴,R² is Ar or a

35

which is unsubstituted or monosubstituted or disubstituted in the phenyl part by A, R³, OR⁴, NH₂, NHA, NA₂, NO₂, CN, Hal, NHCOR⁴, NHSO₂R⁴, COOR⁴, COR⁴, CONHSO₂R⁶, O(CH₂)_nR³, OPh, O(CH₂)_nOR⁴ or S(O)_mR⁴,

5
or a

10

which is unsubstituted or monosubstituted or disubstituted in the cyclohexadienyl part by A, R³, OR⁴, NH₂, NHA, NA₂, NO₂, CN, Hal, NHCOR⁴, NHSO₂R⁴, COOR⁴, COR⁴, CONHSO₂R⁶, O(CH₂)_nR³, OPh, O(CH₂)_nOR⁴ or S(O)_mR⁴,

15

R³ is CN, COOH, COOA, CONHSO₂R⁵ or 1H-tetrazol-5-yl,
R⁴ and R⁴ are each, independently of one another, H, A, or phenyl or benzyl, each of which is unsubstituted or monosubstituted by alkoxy,

20

R⁵ is A or Ar,

R⁶ is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR⁵, NH₂, NHA, NA₂, NO₂, CN or Hal,

25

A is alkyl having 1-6 carbon atoms, in which one or two CH₂ groups may be replaced by O or S atoms or by -CR⁴=CR⁴- groups and in addition 1-7 H atoms may be replaced by F, or benzyl,

30

Ar is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR⁴, NH₂, NHA, NA₂, NO₂, CN, Hal, NHCOR⁴, NHSO₂R⁴, COOR⁴, COR⁴, CONHSO₂R⁶, O(CH₂)_nR³, OPh, O(CH₂)_nOR⁴ or S(O)_mR⁴,

35

Het is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/or S atoms, bonded via N or C, which may be

- 19 -

unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, R³, NH₂, NHA, NA₂, CN, NO₂ and/or carbonyl oxygen,

D is carbonyl or [C(R⁴R⁴)]_n,

5 E is CH₂, S or O,

Hal is F, Cl, Br or I,

X is O or S,

m is 0, 1 or 2,

n is 1 or 2,

10 and their salts;

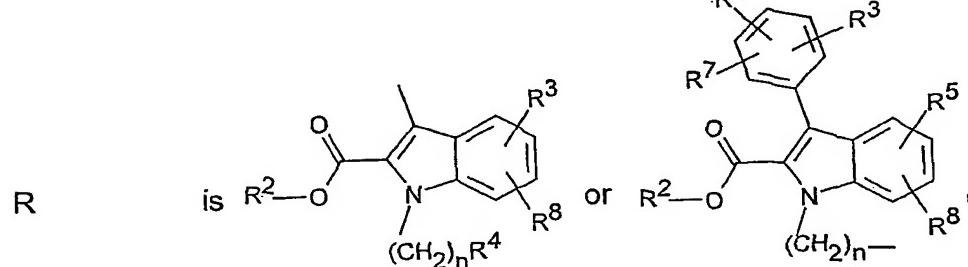
f) the compounds of the formula I described in WO 9719077



I

15 in which

20



25

X is O or S,

R¹ is H, Hal, OH, OA, A, alkylene-O-A, NO₂, NH₂, NH-acyl, SO₂NH₂, SO₃-A, SO₂NHA, CN or formyl,

30 R² is H or A,

R³, R⁵, R⁶

R⁷ and R⁸ are each, independently of one another, H, Hal, OH, OA, O-alkylene-R⁴, A, S-A, NO₂, NH₂, NHA, NA₂,

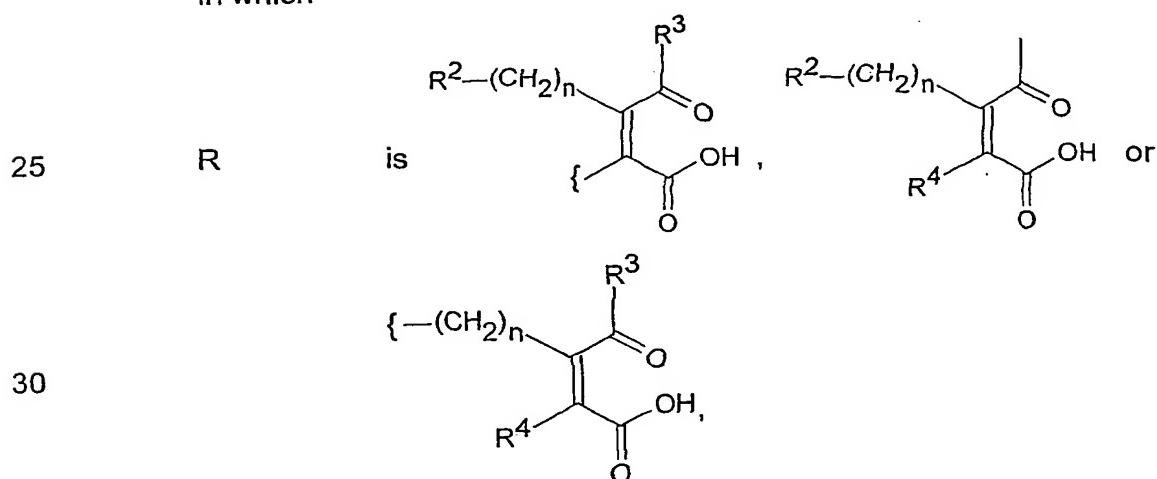
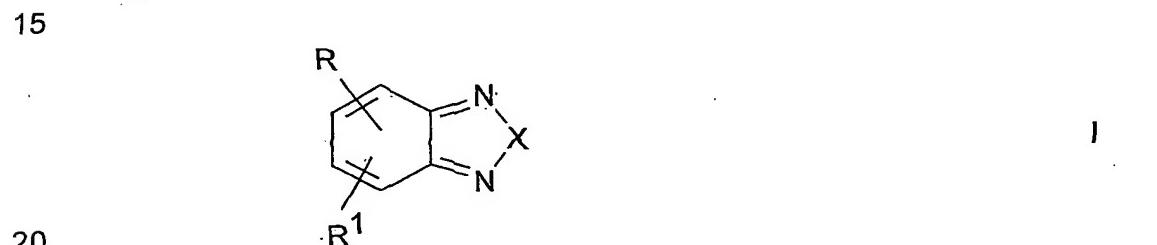
35 NH-acyl, NHSO₂A, NHSO₂R⁴, NASO₂A, NASO₂-R⁴, NH(CO)NH₂, NH(CO)NHA, formyl, NH(CO)NH-phenyl,

- 20 -

NHCOOA, NA-acyl, NHR⁴, NHCOOR⁴, NHCOO-benzyl,
 NSO₂-benzyl, NHCOO-alkylene-OA, NH(CO)NA₂,
 N-piperidinyl-CO-NH, N-pyrrolidinyl-CONH,
 O(CH₂)_nCOOR², O(CH₂)_nOR², CH₂OH or CH₂OA,

5 R³ and R⁶ together are alternatively -O-CH₂-O-, -O-CH₂-CH₂-O-,
 -O-CH₂-CH₂-O- or -O-CF₂-O- or -O-CF₂-CF₂-O-,
 R⁴ is phenyl which is unsubstituted or monosubstituted or
 polysubstituted by R³ and/or R⁶,
 A is alkyl having 1-6 carbon atoms,
 10 Hal is fluorine, chlorine, bromine or iodine,
 n is 1 or 2,
 and their salts;

15 g) the compounds of the formula I described in WO 9730982



R², R³
and R⁴

are each, independently of one another, a phenyl group
which is unsubstituted or monosubstituted or polysubsti-
tuted by Hal, OH, OA, O-alkylene-R⁵, A, S-A, SOA,
SO₂A, SOR⁵, SO₂R⁵, NO₂, NH₂, NHA, NA₂, NH-acyl,
NHSO₂A, NHSO₂R⁵, NASO₂A, NASO₂-R⁵, NH(CO)NH₂,
NH(CO)NHA, formyl, NH(CO)NHR⁵, NHCOOA, NA-acyl,
NHCOOCH₂R⁵, NHSO₂CH₂R⁵, NHCOO-alkylene-OA,
NH(CO)NA₂, 1-piperidinyl-CO-NH, 1-pyrrolidinyl-CONH,
O(CH₂)_nCOOA, O(CH₂)_nCOOH, O(CH₂)_nOH, O(CH₂)_nOA,
CH₂OH, CH₂OA, COOH, COOA, CH₂COOH or
CH₂COOA,

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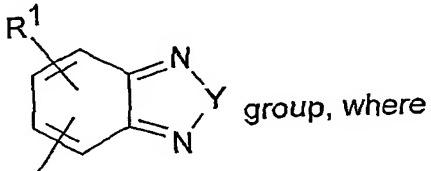
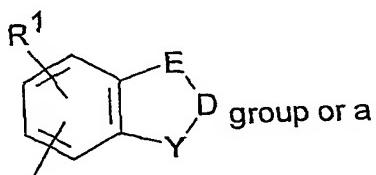
35

R⁵

A

D

or is a



R² is additionally A or cycloalkyl,
is a phenyl group which is unsubstituted or monosubsti-
tuted or polysubstituted by Hal, OH, OA, A, S-A, NO₂,
NH₂, NHA, NA₂, NH-acyl, NHSO₂A, NASO₂A,
NH(CO)NH₂, NH(CO)NHA, formyl, NHCOOA, NA-acyl,
NHCOO-alkylene-OA, NH(CO)NA₂, N-piperidinyl-CO-
NH, N-pyrrolidinyl-CONH, O(CH₂)_nCOOA,
O(CH₂)_nCOOH, O(CH₂)_nOH, O(CH₂)_nOA, CH₂OH,
CH₂OA, COOH, COOA, CH₂COOH or CH₂COOA,

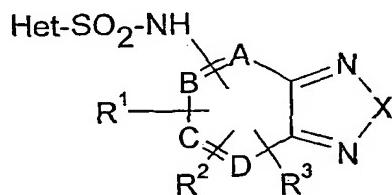
is alkyl having 1-6 carbon atoms, in which one or two
CH₂ groups may be replaced by O or S atoms or by
-CR⁶=CR⁶- groups and/or 1-7 H atoms may be replaced

by F,

is carbonyl or [C(R⁶R⁶)]_m,

- E is CH_2 , S or O,
Y is O or S,
R⁶ and R^{6'} are each, independently of one another, H, F or A,
Hal is fluorine, chlorine, bromine or iodine,
5 n is 1 or 2, and
m is 1 or 2,
or a tautomeric cyclised form, and the (E)-isomers and the salts of all
isomers;
- 10 h) the compounds of the formula I described in WO 9730996

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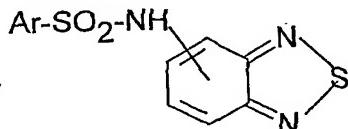
35

- in which
-A=B-C=D- is a -CH=CH-CH=CH- group, in which, in addition, 1 or
2 CH may be replaced by N,
Het is a monocyclic or bicyclic, saturated, unsaturated or
aromatic heterocyclic radical having from 1 to 4 N, O
and/or S atoms which is unsubstituted or substituted by
-Z-R⁶,
R¹, R²
and R³ are each, independently of one another, absent, H, Hal,
A, CF₃, NO₂, NR⁴R⁵, CN, COOR⁴ or NHCOR⁴,
R⁴ and R⁵ are each, independently of one another, H or A, or
together are alternatively -CH₂-(CH₂)_n-CH₂-,
R⁶ is a phenyl radical, benzothiadiazol-5-yl or benzoxa-
diazol-5-yl radical, each of which is unsubstituted or
monosubstituted, disubstituted or trisubstituted by R⁷, R⁸
and/or R⁹,
R⁷, R⁸
and R⁹ are each, independently of one another, A, O-A, CN,
COOH, COOA, Hal, formyl, -CO-A, and R⁷ and R⁸ are
alternatively -O-(CH₂)_m-O-,
A is alkyl having from 1 to 6 carbon atoms,

- 23 -

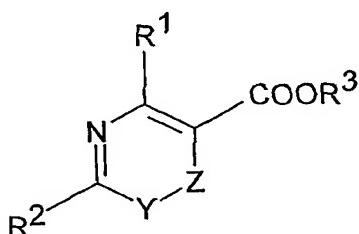
X is O or S,
 Z is -CO-, -CONH-, -CO-(CH₂)_n-, -CH=CH-, -(CH₂)_n-,
 -CONHCO-, -NHCONH-, -NHCOO-, -O-CONH-, -CO-O-
 or -O-CO-,
 5 Hal is F, Cl, Br or I,
 m is 1 or 2, and
 n is 1, 2 or 3,
 and their salts;

10 i) the compounds of the formula I described in DE 19609597



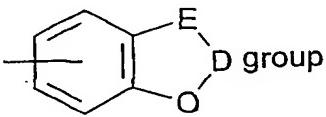
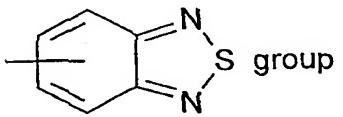
15 in which
 Ar is naphthyl which is monosubstituted by NH₂, NHA or
 NA₂, and
 A is alkyl having from 1 to 6 carbon atoms,
 20 and their physiologically acceptable salts;

j) the compounds of the formula I described in DE 19612101



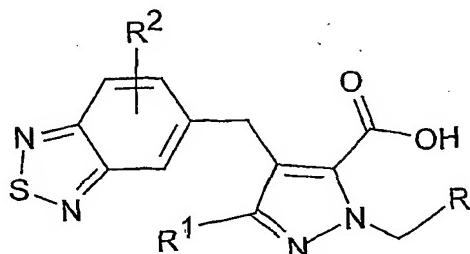
25 in which
 -Y-Z- is -NR⁴-CO or -N=CR⁵-,
 R¹ is Ar,
 R² is H, alkyl having 1-6 carbon atoms which is unsubstituted or monosubstituted, disubstituted or trisubstituted by
 30 OR³ or Hal, or (CH₂)_mPh or (CH₂)_m-cycloalkyl, each of
 35

- 24 -

- which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R³, OR³ or Hal,
- R³ and R^{3'} are each, independently of one another, H, alkyl having 1-6 carbon atoms or benzyl,
- 5 R⁴ is CH₂Ar,
- R⁵ is OCH₂Ar,
- Ar is phenyl which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R⁶, R⁷ or R⁸, or a
- 10 
- which is unsubstituted or monosubstituted in the phenyl part by R⁶, or a
- 15 
- 20 which is unsubstituted or monosubstituted in the cyclohexadienyl part by R⁶,
- E is CH₂ or O,
- D is carbonyl or (CH₂)_n,
- E and D together are alternatively CH=CR⁹,
- 25 R⁶, R^{6'} are each, independently of one another, R³, OR³ or Hal,
- R⁷ is R³, OR³, Hal, NO₂, NH₂, NHR³, NR³R^{3'}, NHCOR³, COOR³, O(CH₂)_nR³ or O(CH₂)_nOR³,
- R⁸ is Ph which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R³, OR³, Hal, NO₂, NH₂, NHR⁶, NR⁶R^{6'}, NHCOR³ or COOR³,
- 30 R⁹ is H, OH, CH₂OH or COOR³,
- Hal is F, Cl, Br or I,
- Ph is phenyl,
- m is 0 or 1,
- 35 n is 1 or 2,
- and their salts;

- 25 -

k) the compounds of the formula I described in WO 9827091



10 in which

R is phenyl which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R³, R⁴ or R⁵, or 2,1,3-benzothiadiazolyl which is unsubstituted or mono-substituted by R²,

15 R¹ is A, in which 1-7 H atoms may be replaced by F, is -S-A, -O-A, is phenyl or -alkylene-phenyl, each of which is unsubstituted or monosubstituted by R³, or is thieryl which is unsubstituted or monosubstituted by R³,

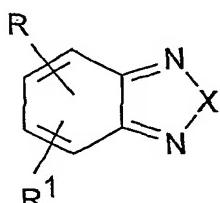
R² is A, F, Cl, Br or -O-A,

20 R³, R⁴ and R⁵ are each, independently of one another, A, -O-A, -S-A, -O-alkylene-COOH, -alkylene-COOH or COOH,

R³ and R⁴ together are alternatively -O-CH₂-O-, and A is alkyl having 1-7 carbon atoms,

25 and their salts;

l) the compounds of the formula I described in WO 9827077



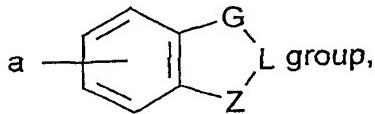
in which

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- 26 -

5	R is	
10		
15	X is O or S, R^1 is H, Hal, OH, OA, A, alkylene-O-A, NO₂, NH₂, NH-acyl, SO₂NH₂, SO₃-A, SO₂NHA, CN or formyl,	
20	R^2 , R^3 and R^4 are each, independently of one another, a phenyl group which is unsubstituted or monosubstituted or polysubstituted by R^7 , where R^2 is additionally A or cycloalkyl, or are	
25		
30		
35		with the proviso that at least one of the radicals R^2 , R^3 or R^4 is an R^8 radical which is unsubstituted or mono-substituted or polysubstituted by R^7 ,
	R^5	is a phenyl group which is unsubstituted or monosubstituted or polysubstituted by Hal, OH, OA, A, S-A, NO₂, NH₂, NHA, NA₂, NH-acyl, NHSO₂A, NASO₂A,

- 27 -

- NH(CO)NH₂, NH(CO)NHA, formyl, NHCOOA, NA-acyl,
NHCOO-alkylene-OA, NH(CO)NA₂, N-piperidinyl-CO-
NH, N-pyrrolidinyl-CONH, O(CH₂)_nCOOA,
O(CH₂)_nCOOH, O(CH₂)_nOH, O(CH₂)_nOA, CH₂OH,
CH₂OA, COOH, COOA, CH₂COOH or CH₂COOA,
- 5 A is alkyl having 1-6 carbon atoms, in which one or two
 CH₂ groups may be replaced by O or S atoms or by
 -CR⁶=CR^{6'}- groups and/or 1-7 H atoms may be replaced
 by F,
- 10 D is carbonyl or [C(R⁶R^{6'})]_m,
- E is CH₂, S or O,
- Y is O or S,
- R⁶ and R^{6'} are each, independently of one another, H, F or A,
 R⁷ is Hal, OH, OA, O-alkylene-R⁵, A, S-A, S-OA, SO₂A,
 S-OR⁵, SO₂R⁵, NO₂, NH₂, NHA, NA₂, NH-acyl, NSO₂A,
 NHSO₂R⁵, NASO₂A, NASO₂-R⁵, NH(CO)NH₂,
 NH(CO)NHA, formyl, NH(CO)NHR⁵, NHCOOA, NA-acyl,
 NHCOOCH₂R⁵, NSO₂CH₂R⁵, NHCOO-alkylene-OA,
 NH(CO)NA₂, 1-piperidinyl-CO-NH, 1-pyrrolidinyl-CONH,
 O(CH₂)_nCOOA, O(CH₂)_nCOOH, O(CH₂)_nOH, O(CH₂)_nOA,
 CH₂OH, CH₂OA, COOH, COOA, CH₂COOH or
 CH₂COOA,
- 15 R⁸ is a 5-7-membered heterocyclic radical having 1-4 N, O
 and/or S atoms or is
- 20 G and Z are each, independently of one another, -CH=, N, O or
 S,
 L is -CH=, -CH=CH- or -CH₂-CH₂-CH₂-,
 Hal is fluorine, chlorine, bromine or iodine,
 n is 0, 1 or 2, and
 m is 1 or 2,
- 25 
- 30 G and Z are each, independently of one another, -CH=, N, O or
 S,
 L is -CH=, -CH=CH- or -CH₂-CH₂-CH₂-,
 Hal is fluorine, chlorine, bromine or iodine,
 n is 0, 1 or 2, and
 m is 1 or 2,
- 35 m is 1 or 2,

or a tautomeric cyclised form, and the (E)-isomers and the salts of all isomers;

- m) the compounds of the formula I described in WO 9841515

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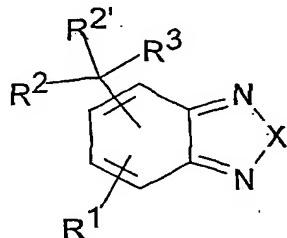
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in which

X is O or S,

R¹ is H, Hal, OH, OA, A, NO₂, NH₂, NHA, NAA', NHCOR⁴, NHCOR⁶, NSO₂R⁴, NSO₂R⁶, S(O)_mR⁶, SO₃H, SO₂NR⁴R⁴ or formyl,

R² and R^{2'} are each, independently of one another, A, (CH₂)_nAr, (CH₂)_nHet, CH₂COAr, CH₂COHet or OAr,

R^{2'} is additionally also H,

R³ is COOR⁴, CN, 1H-tetrazol-5-yl or CONHSO₂R⁵,

R⁴ and R^{4'} are each, independently of one another, H or A,

R⁵ is A or Ar,

R⁶ is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, NH₂, NHA, NAA', NO₂, CN or Hal,

R⁷ and R^{7'} are each, independently of one another, H or alkyl having 1-6 carbon atoms,

A and A' are each, independently of one another, alkyl having 1-6 carbon atoms, in which one or two CH₂ groups may be replaced by O or S atoms or by -CR⁷=CR^{7'}- groups and/or 1-7 H atoms may be replaced by F, or benzyl,

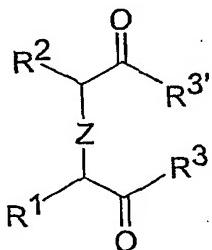
Ar is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR⁴, NH₂, NHA, NAA', NO₂, CN, Hal, NHCOR⁴,

- 29 -

NHCOR⁶, NHSO₂R⁴, NSO₂R⁶, COOR⁴, OPh, CONH₂, CONHA, CONAA', COR⁴, CONHSO₂R⁴, CONHSO₂R⁶, O(CH₂)_nCOOR⁴, O(CH₂)_nOR⁴, SO₃H, SO₂NR⁴R^{4'}, S(O)_mR⁶ or S(O)_mR⁴,

- 5 Het is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having 1-4 N, O and/or S atoms, bonded via N or C, which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, R³, NH₂, NHA, NAA', NO₂ and/or =O,
- 10 Hal is fluorine, chlorine, bromine or iodine,
- m is 0, 1 or 2, and
- n is 1 or 2,
where, if R² is CH₂COAr and R^{2'} is H, R³ is not COOA, and salts thereof;
- 15 n) the compounds of the formula I described in WO 9841521

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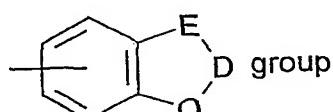
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in which

25 Z is a single or double bond,

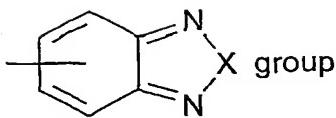
 R¹ is a

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which is unsubstituted or monosubstituted in the phenyl part by R⁷, or is a

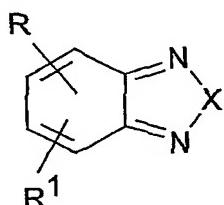
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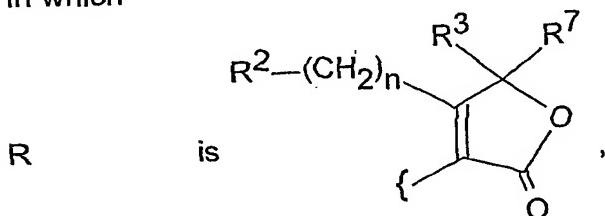
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|------------------------------------|--|
| 5 | which is unsubstituted or monosubstituted in the cyclohexadienyl part by R ⁷ , |
| R ² | is A, Ar-(CH ₂) _m , cycloalkyl-(CH ₂) _m , Het-(CH ₂) _m or R ¹ -(CH ₂) _m , |
| R ³ and R ^{3'} | are each, independently of one another, OR ⁴ , NHSO ₂ R ⁵ , NH ₂ , NHA or NAA', |
| 10 | R ³ and R ^{3'} together are alternatively -O-, forming a cyclic anhydride, |
| R ⁴ and R ^{4'} | are each, independently of one another, H or A, |
| R ⁵ | is A or Ar, |
| R ⁶ | is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, NH ₂ , NHA, NAA', NO ₂ , CN or Hal, |
| 15 | |
| R ⁷ | is A, COOR ⁴ , CN, 1H-tetrazol-5-yl, CONHSO ₂ R ⁵ , Hal, OR ⁴ , NO ₂ , NH ₂ , NHA, NAA', NHCOR ⁴ , NHCOR ⁶ , NHSO ₂ R ⁴ , NHSO ₂ R ⁶ , S(O) _k R ⁴ , S(O) _k R ⁶ , SO ₂ NR ⁴ R ^{4'} or formyl, |
| R ⁸ and R ^{8'} | are each, independently of one another, H or alkyl having |
| 20 | 1-6 carbon atoms, |
| E | is CH ₂ or O, |
| D | is carbonyl or (CR ⁴ R ^{4'}) _n , |
| E and D | together are alternatively CR ⁴ =R ^{4'} , |
| X | is S or O, |
| 25 | A and A' are each, independently of one another, alkyl having 1-6 carbon atoms, in which one or two CH ₂ groups may be replaced by O or S atoms or by -CR ⁸ =CR ^{8'} - groups and/or 1-7 H atoms may be replaced by F, or benzyl, |
| 30 | Ar is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR ⁴ , NH ₂ , NHA, NAA', NO ₂ , CN, Hal, NHCOR ⁴ , NHCOR ⁶ , NHSO ₂ R ⁴ , NHSO ₂ R ⁶ , COOR ⁴ , OPh, CONH ₂ , CONHA, CONAA', COR ⁴ , CONHSO ₂ R ⁴ , CONHSO ₂ R ⁶ , O(CH ₂) _n COOR ⁴ , O(CH ₂) _n OR ⁴ , SO ₂ NR ⁴ R ^{4'} , S(O) _k R ⁶ or S(O) _k R ⁴ , |
| 35 | |

Het is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having 1-4 N, O and/or S atoms, bonded via N or C, which may be unsubstituted, monosubstituted or disubstituted or trisubstituted by Hal, A, COOR⁴, CN, 1H-tetrazol-5-yl, CONHSO₂R⁵, NH₂, NHA, NAA', NO₂ and/or =O,
 Hal is fluorine, chlorine, bromine or iodine,
 k is 0, 1 or 2,
 m is 0, 1 or 2, and
 n is 1 or 2,
 and the (Z)- and (E)-isomers and the salts of all isomers;

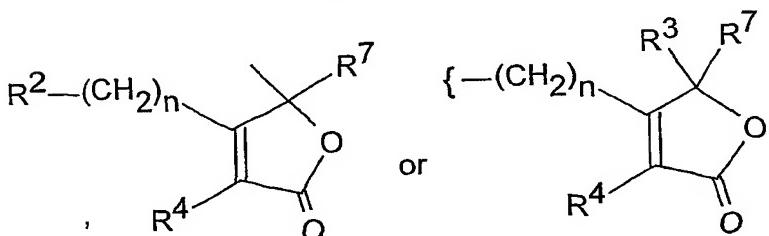
- o) the compounds of the formula I described in WO 9842702



in which



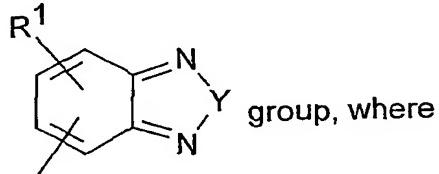
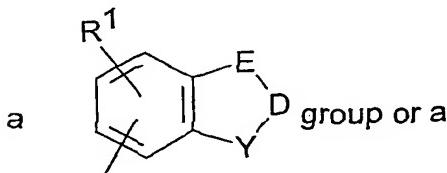
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30

X and **Y** are each, independently of one another, O or S,
R¹ is H, Hal, OH, OA, A, alkylene-O-A, NO₂, NH₂, NH-acyl,
SO₂NH₂, SO₂-A, SO₂NHA, CN or formyl,
R², R³

and R⁴ are each, independently of one another, a phenyl group which is unsubstituted or monosubstituted or polysubstituted by Hal, OH, OA, O-alkylene-R⁵, A, S-A, S-OA, SO₂A, S-OR⁵, SO₂R⁵, NO₂, NH₂, NHA, NA₂, NH-acyl, 5 NHSO₂A, NHSO₂R⁵, NASO₂A, NASO₂-R⁵, NH(CO)NH₂, NH(CO)NHA, formyl, NH(CO)NHR⁵, NHCOOA, NA-acyl, 10 NHCOOCH₂R⁵, NHSO₂CH₂R⁵, NHCOO-alkylene-OA, NH(CO)NA₂, 1-piperidinyl-CO-NH, 1-pyrrolidinyl-CONH, O(CH₂)_nCOOA, O(CH₂)_nCOOH, O(CH₂)_nOH, O(CH₂)_nOA, CH₂OH, CH₂OA, COOH, COOA, CH₂COOH or 15 CH₂COOA,



R² is additionally A or cycloalkyl,
R⁵ is a phenyl group which is unsubstituted or monosubstituted or polysubstituted by Hal, OH, OA, A, S-A, NO₂, 25 NH₂, NHA, NA₂, NH-acyl, NHSO₂A, NASO₂A, NH(CO)NH₂, NH(CO)NHA, formyl, NHCOOA, NA-acyl, NHCOO-alkylene-OA, NH(CO)NA₂, N-piperidinyl-CO-NH, N-pyrrolidinyl-CONH, O(CH₂)_nCOOA, O(CH₂)_nCOOH, O(CH₂)_nOH, O(CH₂)_nOA, 30 CH₂OH, CH₂OA, COOH, COOA, CH₂COOH or CH₂COOA,

35

A is alkyl having 1-6 carbon atoms, in which one or two CH₂ groups may be replaced by O or S atoms or by -CR⁶=CR⁶- groups and/or 1-7 H atoms may be replaced by F,

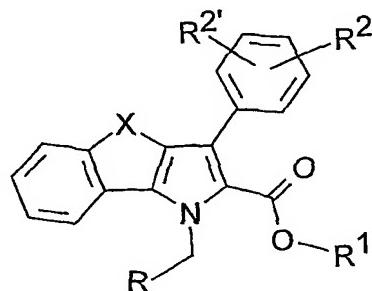
D is carbonyl or [C(R⁶R⁶)]_m,

- 33 -

- E is CH_2 , S or O,
 R⁶ and R⁸ are each, independently of one another, H, F or A,
 R⁷ is $-\text{O}-\text{C}(=\text{Y})-\text{NH}-\text{R}^8$,
 R⁸ is alkyl having 1-10 carbon atoms which is unsubstituted
 or monosubstituted or disubstituted by R⁸ and in which
 1-2 carbon atoms may be replaced by O and/or S,
 and/or may be substituted by =O,
 or
 cycloalkyl, in which 1-2 carbon atoms may be replaced
 by N, O and/or S,
- R⁹ is phenyl which is unsubstituted or monosubstituted or
 disubstituted by Hal,
 or is naphthyl, A-O-C(=O)- or Hal,
 Hal is fluorine, chlorine, bromine or iodine,
 n is 0, 1 or 2, and
 m is 1 or 2,
 and salts thereof;

p) the compounds of the formula I described in WO 9842709

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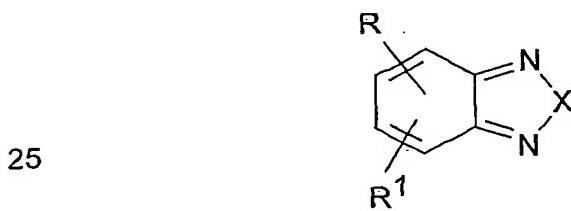
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in which

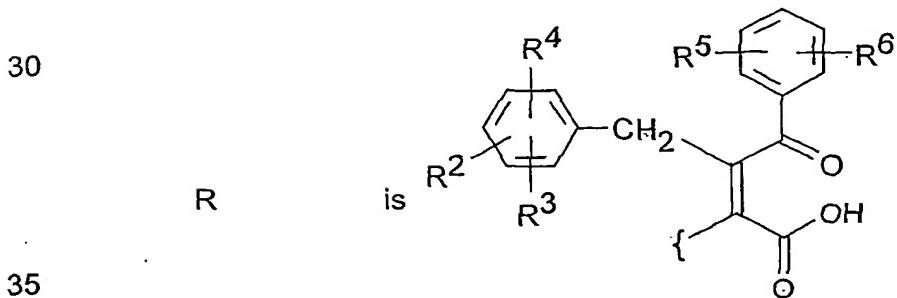
- X is N-R³, O or S,
 R is 2,1,3-benzothiadiazol-4- or 5-yl or 2,1-benzoiso-thiazol-5- or 6-yl, each of which is unsubstituted or monosubstituted or disubstituted by R² and/or R^{2'},
 or
 phenyl which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R² and/or R^{2'},
 R¹ is H or A,

- 34 -

- R² and R^{2'} are each, independently of one another, H, A, OH, OA, Hal, OCF₃, OCHF₂, -O-CO-A, -O-alkylene-COOR¹, -O-alkylene-CH₂-OR¹, or
- 5 OCH₂-phenyl or -O-CO-phenyl, each of which is unsubstituted or monosubstituted or disubstituted in the phenyl part by R⁴ and/or R^{4'},
- R² and R^{2'} together are alternatively -OCH₂O-, -OCH₂CH₂O- or -OCH₂CH₂-,
- 10 R³ is H, A, alkylene-O-A, -CO-OA, or alkylene-phenyl which is unsubstituted or mono-substituted or disubstituted in the phenyl part by R⁴ and/or R^{4'},
- 15 R⁴ and R^{4'} are each, independently of one another, H, A, OH, OA, Hal, COOR¹ or CH₂OR¹,
- A is alkyl having 1-6 carbon atoms,
- Hal is fluorine, chlorine, bromine or iodine, and their salts;
- 20 q) the compounds of the formula I described in WO 9905132



in which



	X	is O or S,
	R ¹	is H, Hal, OA or A,
	R ² , R ³ R ⁵ , and R ⁶	are each, independently of one another, H, Hal, A, OA or R ⁴ ,
5	R ⁴	is -O-(CH ₂) _n -Cy,
	Cy	is cycloalkyl having 3-8 carbon atoms,
	A	is alkyl having 1-6 carbon atoms, in which one or two CH ₂ groups may be replaced by O or S atoms or by -CR ⁵ =CR ⁵ - groups and/or 1-7 H atoms may be replaced by F,
10	R ⁵ and R ^{5'}	are each, independently of one another, H, F or A,
	Hal	is fluorine, chlorine, bromine or iodine,
	n	is 0, 1 or 2,
15		or a tautomeric cyclised form, and the (E)-isomers and the salts of all isomers.

The phosphodiesterase V inhibitors of the formula I and also the starting materials for their preparation are, in addition, prepared by methods known per se, as described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise under reaction conditions which are known and suitable for the said reactions. Use can also be made here of variants which are known per se, but are not mentioned here in greater detail.

In the compounds of the formulae II or III, R¹, R², R³, R⁴ and X have the meanings indicated, in particular the preferred meanings indicated.

- 30 If L is a reactive esterified OH group, this is preferably alkylsulfonyloxy having 1-6 carbon atoms (preferably methylsulfonyloxy) or arylsulfonyloxy having 6-10 carbon atoms (preferably phenyl- or p-tolylsulfonyloxy, furthermore also 2-naphthalenesulfonyloxy).
- 35 The compounds of the formula I can preferably be obtained by reacting compounds of the formula II with compounds of the formula III.

If desired, the starting materials can also be formed in situ by not isolating them from the reaction mixture, but instead immediately converting them further into the compounds of the formula I.

On the other hand, it is possible to carry out the reaction stepwise.

5

The starting compounds of the formulae II and III are generally known. If they are not known, they can be prepared by methods known per se.

Compounds of the formula II can be prepared by methods known from the literature, for example from 4-amino-3-alkoxycarbonylpyrazoles by cyclisation using nitriles followed by reaction of the cyclisation products with phosphorus oxychloride (analogously to Houben Weyl E9b/2).

10

In detail, the reaction of the compounds of the formula II with the compounds of the formula III is carried out in the presence or absence of an inert solvent at temperatures between about -20 and about 150°, preferably between 20 and 100°.

15

The addition of an acid-binding agent, for example an alkali or alkaline earth metal hydroxide, carbonate or bicarbonate or another salt of a weak acid of the alkali or alkaline earth metals, preferably of potassium, sodium or calcium, or the addition of an organic base, such as triethylamine, dimethylamine, pyridine or quinoline, or of an excess of the amine component, may be favourable.

20

Examples of suitable inert solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, di-isopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide, N-methylpyrrolidone or dimethylformamide (DMF); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the said solvents.

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It is furthermore possible to convert a radical X in a compound of the formula I into another radical X, for example by hydrolysing an ester or a cyano group to give a COOH group.

- 5 Ester groups can be saponified, for example, using NaOH or KOH in water, water/THF or water/dioxane at temperatures between 0 and 100°. Carboxylic acids can be converted into the corresponding carbonyl chlorides, for example using thionyl chloride, and these can be converted into carboxamides. Elimination of water therefrom in a known manner
10 gives carbonitriles.

An acid of the formula I can be converted into the associated acid-addition salt using a base, for example by reaction of equivalent amounts of the acid and the base in an inert solvent, such as ethanol, followed by evaporation. Suitable bases for this reaction are, in particular, those which give physiologically acceptable salts.

- 15 Thus, the acid of the formula I can be converted into the corresponding metal salt, in particular alkali metal or alkaline earth metal salt, or into the corresponding ammonium salt using a base (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate).
20 Also suitable for this reaction are, in particular, organic bases which give physiologically acceptable salts, such as, for example, ethanolamine.

On the other hand, a base of the formula I can be converted into the
25 associated acid-addition salt using an acid, for example by reaction of equivalent amounts of the base and the acid in an inert solvent, such as ethanol, followed by evaporation. Suitable acids for this reaction are, in particular, those which give physiologically acceptable acids. Thus, it is possible to use inorganic acids, for example sulfuric acid, nitric acid, hydro-
30 halic acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as orthophosphoric acid, or sulfamic acid, furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, for example formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid,
35 malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid,

nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenemono- and -disulfonic acids, or laurylsulfuric acid. Salts with physiologically unacceptable acids, for example picrates, can be used for the isolation and/or purification of the compounds of the formula I.

The invention furthermore relates to the pharmaceutical formulations comprising at least one phosphodiesterase V inhibitor of the formula I and/or one of its physiologically acceptable salts and at least one endothelin receptor antagonist and comprising one or more excipients and/or assistants.

The pharmaceutical preparations are prepared, in particular, by non-chemical methods, in which the active ingredients are converted into a suitable dosage form together with at least one solid, liquid and/or semi-liquid excipient or assistant.

These preparations can be used as medicaments in human or veterinary medicine. Suitable excipients are organic or inorganic substances which are suitable for enteral (for example oral), parenteral or topical administration and do no react with the novel compounds, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatine, carbohydrates, such as lactose or starch, magnesium stearates, talc or Vaseline. Suitable for oral administration are, in particular, tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops, suitable for rectal administration are suppositories, suitable for parenteral administration are solutions, preferably oil-based or aqueous solutions, furthermore suspensions, emulsions or implants, and suitable for topical application are ointments, creams or powders. The novel compounds may also be lyophilised and the resultant lyophilisates used, for example, for the preparation of injection preparations. The preparations indicated may be sterilised and/or comprise assistants, such as lubricants, preservatives, stabilisers and/or wetting agents, emulsifiers, salts for modifying the osmotic pressure, buffer substances, colorants, flavours and/or a plurality of further active ingredients, for example one or more vitamins. They can furthermore be administered as nasal sprays.

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In general, the substances are preferably administered in doses of between about 1 and 500 mg, in particular between 5 and 100 mg, per dosage unit. The daily dose is preferably between about 0.02 and

5 10 mg/kg of body weight. However, the specific dose for each patient depends on a wide variety of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and method of administration, on the excretion rate, medicament combination and severity of the particular
10 illness to which the therapy applies. Oral administration is preferred.

The invention therefore also relates to the use of the pharmaceutical preparations described for the preparation of a medicament for the treatment of angina, high blood pressure, high pulmonary pressure,
15 congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cor pulmonale, dextrocardiac insufficiency, atherosclerosis, conditions of reduced patency of the heart vessels, peripheral vascular diseases, strokes, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, irritable bowel syndrome, tumours, renal insufficiency,
20 liver cirrhosis, erectile dysfunction and for the treatment of female sexual disorders.

The invention relates, in particular, to the use of the formulations according to the invention for the preparation of a medicament for the treatment of high pulmonary pressure, congestive heart failure (CHF), chronic
25 obstructive pulmonary disease (COPD), cor pulmonale and/or dextrocardiac insufficiency.

The constituents of the novel pharmaceutical [preparation] are preferably administered combined. However, they can also be administered individually at the same time or successively.

The invention also relates to a set (kit) consisting of separate packs of
30 (a) an effective amount of [7-(3-chloro-4-methoxybenzylamino)-1-methyl-
35 3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy]acetic acid and/or physiologically acceptable salts and/or solvates thereof

and

- (b) an effective amount of an endothelin receptor antagonist.

The set comprises suitable containers, such as boxes, individual bottles,
5 cartons, bags or ampoules. The set may comprise, for example, separate
ampoules each containing an effective amount of [7-(3-chloro-4-methoxy-
benzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy]-
acetic acid, and/or physiologically acceptable salts and/or solvates thereof
and of the endothelin receptor antagonist in dissolved or lyophilised form.
10

Above and below, all temperatures are given in °C. In the following
examples, "conventional work-up" means that water is added if necessary,
the pH is adjusted, if necessary, to between 2 and 10, depending on the
constitution of the end product, the mixture is extracted with ethyl acetate
15 or dichloromethane, the phases are separated, the organic phase is dried
over sodium sulfate and evaporated, and the product is purified by chro-
matography on silica gel and/or by crystallisation.
20

Mass spectrometry (MS): EI (electron impact ionisation) M⁺
FAB (fast atom bombardment) (M+H)⁺

Example 1

3 g of methyl 3-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-
25 yl]propionate and 1.9 g of 3-chloro-4-methoxybenzylamine ("A") in 50 ml of
dimethylformamide (DMF) is stirred for 12 hours at 60° in the presence of
potassium carbonate. After filtration, the solvent is removed, and the pro-
duct is subjected to conventional work-up, giving 4.6 g of methyl 3-[7-(3-
chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-
30 pyrimidin-5-yl]propionate as a colourless oil.

Analogous reaction of "A"

with methyl 2-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-
35 yl]acetate gives

methyl 2-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]acetate.

Analogous reaction of 3,4-methylenedioxybenzylamine

5

with methyl 3-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]propionate gives

methyl 3-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]propionate.

10

Analogous reaction of "A"

with methyl 4-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyrate gives

15

methyl 4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyrate.

Analogous reaction of 3,4-methylenedioxybenzylamine

20

with methyl 4-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyrate gives

methyl 4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyrate.

25

Analogous reaction of "A"

with methyl 5-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]valerate gives

30

methyl 5-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]valerate.

Analogous reaction of 3,4-methylenedioxybenzylamine

35

with methyl 5-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]valerate gives

- 42 -

methyl 5-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]valerate.

Analogous reaction of "A"

5

with methyl 7-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]heptanoate gives

methyl 7-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]heptanoate.

10

Analogous reaction of 3,4-methylenedioxybenzylamine

with methyl 7-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]heptanoate gives

15

methyl 7-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]heptanoate.

Analogous reaction of "A"

20

with methyl 2-[4-(7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl)-cyclohex-1-yl]acetate gives

methyl 2-{4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexyl-1-yl}acetate.

25

Analogous reaction of 3,4-methylenedioxybenzylamine

with methyl 2-[4-(7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl)-cyclohex-1-yl]acetate gives

30

methyl 2-{4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexyl-1-yl}acetate.

Analogous reaction of benzylamine

35

with methyl 3-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]propionate gives

- 43 -

methyl 3-[7-benzylamino-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-yl]propionate;

with methyl 4-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyrate gives

methyl 4-[7-benzylamino-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-yl]butyrate;

with methyl 5-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]valerate gives

methyl 5-[7-benzylamino-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-yl]valerate.

Analogous reaction of "A"

with methyl 4-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexanecarboxylate gives
methyl 4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexanecarboxylate

and reaction of 3,4-methylenedioxybenzylamine gives
methyl 4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexanecarboxylates.

Example 2

4.3 g of methyl 3-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]propionate are dissolved in 30 ml of tetrahydrofuran (THF), 10 ml of 10% NaOH are added, and the mixture is stirred at 60° for 8 hours. After 10% HCl has been added, the precipitated crystals are separated off and recrystallised from methanol, giving 3.7 g of 3-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]propionic acid, m.p. 178°.

Evaporation with the equivalent amount of methanolic potassium hydroxide solution gives the potassium salt of the acid as an amorphous powder.

- 5 Analogous reaction of the esters listed in Example 1 gives the following compounds:

2-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]acetic acid,

10 3-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]propionic acid,

15 4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid, m.p. 152°;

4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid, m.p. 172°;

20 5-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]valeric acid, m.p. 159°;

25 5-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]valeric acid, ethanolamine salt, m.p. 160°;

7-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]heptanoic acid,

30 7-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]heptanoic acid,

2-[4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexyl-1-yl]acetic acid,

35 2-[4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexyl-1-yl]acetic acid,

3-[7-benzylamino-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]-propionic acid,

5 4-[7-benzylamino-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-
yI]butyric acid,

10 5-[7-benzylamino-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-
yI]valeric acid, m.p. 185°;

15 4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-
pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexanecarboxylic acid,

15 4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-
pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexanecarboxylic acid.

The following compounds are obtained analogously:

20 5-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-isopropyl-1*H*-
pyrazolo[4,3-d]pyrimidin-5-yl]valeric acid, cyclohexylamine salt, m.p. 148°;

4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-ethyl-1*H*-
pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid, m.p. 176°;

25 4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-ethyl-1*H*-
pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid, m.p. 187°;

4-[7-(3-chloro-4-methoxybenzylamino)-1-ethyl-3-methyl-1*H*-
pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid, m.p. 206°;

30 4-[7-(3,4-methylenedioxybenzylamino)-1-ethyl-3-methyl-1*H*-
pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid, m.p. 177°;

35 4-[7-benzylamino-1-methyl-3-ethyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-
yI]butyric acid, m.p. 208°;

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4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-methyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid, m.p. 250°;

5 4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-methyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid, m.p. 225°;

10 4-[7-benzylamino-1-methyl-3-methyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid, m.p. 201°;

15 10 5-[7-(4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-yl]valeric acid, m.p. 160°;

15 15 5-[7-(3-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-yl]valeric acid, m.p. 141°;

20 15 5-[7-(4-chlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-yl]valeric acid, m.p. 148°;

20 20 5-[7-(3-chlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-yl]valeric acid, m.p. 151°;

Example 3

25 A mixture of 1.8 g of methyl 4-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]phenylcarboxylate ("B") and 1.5 g of 3-chloro-4-methoxybenzylamine in 20 ml of N-methylpyrrolidone is heated at 110° for 4 hours. After cooling, the mixture is subjected to conventional work-up, giving 2.2 g of methyl 4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]benzoate.

30 Analogously to Example 2, 1.2 g of the ester give 1.0 g of 4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]benzoic acid, ethanolamine salt, m.p. 139°.

35 Analogously to Example 1, "B" and 3,4-methylenedioxybenzylamine give

- 47 -

methyl 4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]benzoate, and ester hydrolysis thereof gives 4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]benzoic acid.

5

The following compounds are obtained analogously:

4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]phenylacetic acid, glucamine salt, m.p. 114°

10

and

4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]phenylacetic acid.

Example 4

15

1 equivalent of 3-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]propionic acid and 1.2 equivalents of thionyl chloride are stirred in dichloromethane for 2 hours. The solvent is removed, giving 3-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]propionyl chloride.

20

The product is transferred into aqueous ammonia, and the mixture is stirred for one hour and subjected to conventional work-up, giving 3-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-pyrimidin-5-yl]propionamide.

25

Example 5

30

1 equivalent of DMF and 1 equivalent of oxalyl chloride are dissolved in acetonitrile at 0°. 1 equivalent of 3-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]propionamide is then added. The mixture is stirred for a further one hour. Conventional work-up gives 3-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]propionitrile.

35

Example 6

Analogously to Examples 1, 2 and 3, reaction of the corresponding chloropyrimidine derivatives with 3,4-ethylenedioxybenzylamine gives the following carboxylic acids:

5 4-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]butyric acid,

10 3-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]propionic acid,

15 5-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]valeric acid,

20 7-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]heptanoic acid,

25 2-{4-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexyl-1-yl}acetic acid,

30 4-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]cyclohexanecarboxylic acid,

35 4-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]benzoic acid,

40 4-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]benzoic acid,

45 4-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]phenylacetic acid.

Analogous reaction with 3,4-dichlorobenzylamine gives the following compounds:

50 4-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]butyric acid, m.p. 209°;

3-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]propionic acid,

5 5-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]valeric acid,

10 7-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]heptanoic acid,

15 2-{4-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]cyclohexyl-1-yl}acetic acid,

15 4-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]cyclohexanecarboxylic acid,

20 4-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]benzoic acid,

20 4-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]phenylacetic acid.

Analogous reaction with 3-chloro-4-ethoxybenzylamine gives the following compounds:

25 4-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]butyric acid,

30 3-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]propionic acid,

35 5-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]valeric acid,

35 7-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-yl]heptanoic acid,

- 50 -

2-{4-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexyl-1-yl}acetic acid,

5 4-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexanecarboxylic acid,

10 4-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]benzoic acid,

15 4-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]phenylacetic acid.

Analogous reaction with 3-chloro-4-isopropoxybenzylamine gives the
15 following compounds

4-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid,

20 3-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]propionic acid,

25 5-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]valeric acid,

25 7-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]heptanoic acid,

30 2-{4-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexyl-1-yl}acetic acid,

35 4-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]cyclohexanecarboxylic acid,

35 4-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]benzoic acid,

4-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl]phenylacetic acid.

5 Example 7

The following compound is obtained analogously to Examples 1 and 2:

[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]-

10 pyrimidin-5-ylmethoxy]acetic acid, ethanolamine salt, m.p. 138°.

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The examples below relate to pharmaceutical preparations:

Example A: Injection vials

- 5 A solution of 100 g of an active ingredient of the formula I, 100 g of the endothelin receptor antagonist and 5 g of disodium hydrogenphosphate in 3 l of bidistilled water is adjusted to pH 6.5 using 2N hydrochloric acid, sterile filtered, transferred into injection vials, lyophilised under sterile
10 conditions and sealed under sterile conditions. Each injection vial contains 5 mg of each active ingredient.

Example B: Suppositories

- 15 A mixture of 20 g of an active ingredient of the formula I and 20 g of an endothelin receptor antagonist is melted with 100 g of soya lecithin and 1400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of each active ingredient.

20 **Example C: Solution**

- A solution is prepared from 1 g of an active ingredient of the formula I, 1 g of an endothelin receptor antagonist, 9.38 g of $\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$, 28.48 g of $\text{Na}_2\text{HPO}_4 \cdot 12 \text{H}_2\text{O}$ and 0.1 g of benzalkonium chloride in 940 ml of
25 bidistilled water. The pH is adjusted to 6.8, and the solution is made up to 1 l and sterilised by irradiation. This solution can be used in the form of eye drops.

Example D: Ointment

- 30 500 mg of an active ingredient of the formula I and 500 mg of an endothelin receptor antagonist are mixed with 99.5 g of Vaseline under aseptic conditions.

35 **Example E: Tablets**

A mixture of 1 kg of active ingredient of the formula I, 1 g of an endothelin receptor antagonist, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is pressed in a conventional manner to give tablets in such a way that each tablet contains 10 mg of each active
5 ingredient.

Example F: Coated tablets

Tablets are pressed analogously to Example E and subsequently coated in
10 a conventional manner with a coating of sucrose, potato starch, talc, tragacanth and dye.

Example G: Capsules

15 2 kg of active ingredient of the formula I and 2 kg of an endothelin receptor antagonist are introduced in a conventional manner into hard gelatine capsules in such a way that each capsule contains 20 mg of each active ingredient.

20 **Example H: Ampoules**

A solution of 1 kg of active ingredient of the formula I and 1 kg of an endothelin receptor antagonist in 60 l of bidistilled water is sterile filtered, transferred into ampoules, lyophilised under sterile conditions and sealed
25 under sterile conditions. Each ampoule contains 10 mg of each active ingredient.

Example I: Inhalation spray

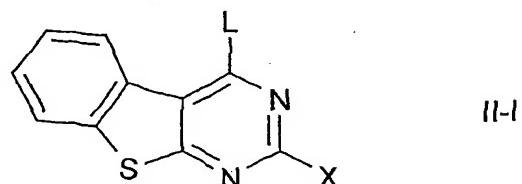
30 14 g of active ingredient of the formula I and 14 g of an endothelin receptor antagonist are dissolved in 10 l of isotonic NaCl solution, and the solution is transferred into commercially available spray containers with pump mechanism. The solution can be sprayed into the mouth or nose. One spray shot (about 0.1 ml) corresponds to a dose of about 0.14 mg of each
35 active ingredient.

Compounds of the formula I-I:

The compounds of the formula I-I according to Claim 1 and their salts are
5 prepared by a process,
characterised in that

- a) a compound of the formula II-I

10



15

in which

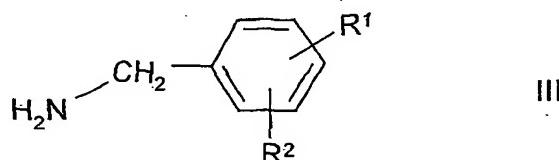
X is as defined above,

20

and L is Cl, Br, OH, SCH₃ or a reactive esterified OH group,

is reacted with a compound of the formula III

25



in which

30

R¹ and R² are as defined above,

or

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- b) a radical X in a compound of the formula I-I is converted into another radical X by, for example, hydrolysing an ester group to a COOH group or converting a COOH group into an amide or into a cyano group,

and/or in that a compound of the formula I-I is converted into one of its salts.

The term solvates of the compounds of the formula I-I is taken to mean adductions of inert solvent molecules onto the compounds of the formula I-II which form owing to their mutual attractive forces. Solvates are, for example, mono- or dihydrates or alcoholates.

Above and below, the radicals R¹, R², R³, R⁴, R⁵, R⁶, R⁷, X and L are as defined for the formulae I-I, II-I and III, unless expressly stated otherwise.

A is alkyl having 1-6 carbon atoms.

In the above formulae, alkyl is preferably unbranched and has 1, 2, 3, 4, 5 or 6 carbon atoms and is preferably methyl, ethyl or propyl, furthermore 15 preferably isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, but also n-pentyl, neopentyl, isopentyl or hexyl.

X is an R⁴, R⁵ or R⁶ radical which is monosubstituted by R⁷.

R⁴ is a linear or branched alkylene radical having 1-10 carbon atoms, where the alkylene radical is preferably, for example, methylene, ethylene, 20 propylene, isopropylene, butylene, isobutylene, sec-butylene, pentylene, 1-propylene, 1,2- or 3-methylbutylene, 1,1-, 1,2- or 2,2-dimethylpropylene, 1-ethylpropylene, hexylene, 1-, 2-, 3- or 4-methylpentylene, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutylene, 1- or 2-ethylbutylene, 1-ethyl-1-methylpropylene, 1-ethyl-2-methylpropylene, 1,1,2- or 1,2,2-trimethylpropylene, linear or branched heptylene, octylene, nonylene or decylene.

R⁵ is furthermore, for example, but-2-enylene or hex-3-enylene.

Very particular preference is given to ethylene, propylene or butylene.

R⁵ is cycloalkylalkylene having 5-12 carbon atoms, preferably, for example, cyclopentylmethylen, cyclohexylmethylen, cyclohexylethylen, cyclohexylpropylene or cyclohexylbutylene.

R⁵ is alternatively cycloalkyl, preferably having 5-7 carbon atoms.

Cycloalkyl is, for example, cyclopentyl, cyclohexyl or cycloheptyl.

Hal is preferably F, Cl or Br, but alternatively I.

The radicals R¹ and R² may be identical or different and are preferably in

the 3- or 4-position of the phenyl ring. They are, for example, each, inde-

5 pendently of one another, H, hydroxyl, alkyl, F, Cl, Br or I or together are alkylene, such as, for example, propylene, butylene or pentylene, furthermore ethyleneoxy, methylenedioxy or ethylenedioxy. They are alternatively preferably each alkoxy, such as, for example, methoxy, ethoxy or propoxy.

10 The radical R⁷ is preferably, for example, COOH, COOCH₃, COOC₂H₅, CONH₂, CON(CH₃)₂, CONHCH₃ or CN.

Throughout the invention, all radicals which occur more than once may be identical or different, i.e. are independent of one another.

15 The invention relates, in particular, to pharmaceutical formulations comprising an endothelin receptor antagonist and at least one compound of the formula I-I in which at least one of the said radicals has one of the preferred meanings indicated above. Some preferred groups of

20 compounds may be expressed by the following sub-formulae Ia to Ie, which conform to the formula I-II and in which the radicals not designated in greater detail are as defined for the formula I-I, but in which

in Ia X is R⁴, phenyl or phenylmethyl, each of which is substituted by COOH, COOA, CONH₂, CONA₂, CONHA or CN;

25 in Ib R¹ and R² together are alkylene having 3-5 carbon atoms, -O-CH₂-CH₂-; -O-CH₂-O- or -O-CH₂-CH₂-O-, is R⁴, phenyl or phenylmethyl, each of which is substituted by COOH, COOA, CONH₂, CONA₂, CONHA or CN;

30 in Ic R¹ and R² are each, independently of one another, H, A, OA or Hal,

- | | | |
|----|--|--|
| | R ¹ and R ² | together are alkylene having 3-5 carbon atoms, -O-CH ₂ -CH ₂ -, -O-CH ₂ -O- or -O-CH ₂ -CH ₂ -O-, |
| 5 | X | is R ⁴ , phenyl or phenylmethyl, each of which is substituted by COOH, COOA, CONH ₂ , CONA ₂ , CONHA or CN; |
| | in Id R ¹ and R ² | are each, independently of one another, H, A, OA or Hal, |
| 10 | R ¹ and R ² | together are alternatively alkylene having 3-5 carbon atoms, -O-CH ₂ -CH ₂ -, -O-CH ₂ -O- or -O-CH ₂ -CH ₂ -O-, |
| | X | is alkylene having 2-5 carbon atoms, cyclohexyl, phenyl or phenylmethyl, each of which is mono-substituted by R ⁷ , |
| 15 | R ⁷ | is COOH or COOA, |
| | A | is alkyl having from 1 to 6 carbon atoms, |
| | Hal | is F, Cl, Br or I; |
| | in Ie R ¹ and R ² | are each, independently of one another, H, A, OA or Hal, |
| 20 | R ¹ and R ² | together are alkylene having 3-5 carbon atoms, -O-CH ₂ -CH ₂ -, -O-CH ₂ -O- or -O-CH ₂ -CH ₂ -O-, |
| | X | is alkylene having 2-5 carbon atoms, cyclohexyl, phenyl or phenylmethyl, each of which is mono-substituted by R ⁷ , |
| 25 | R ⁷ | is COOH or COOA, |
| | A | is alkyl having from 1 to 6 carbon atoms, |
| | Hal | is F, Cl, Br or I. |
| 30 | The invention preferably relates to a formulation comprising [4-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]cyclohexane-carboxylic acid and physiologically acceptable salts and/or solvates thereof and at least one endothelin receptor antagonist. | |
| | Besides the free acid, the ethanolamine salt is preferred. | |
| 35 | Preferred endothelin receptor antagonists are those listed above under the PDE V inhibitors of the formula I. | |

- The phosphodiesterase V inhibitors of the formula I-I and also the starting materials for their preparation are, in addition, prepared by methods known per se, as described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise under reaction conditions which are known and suitable for the said reactions. Use can also be made here of variants which are known per se, but are not mentioned here in greater detail.
- In the compounds of the formulae II-I or III, R¹, R², R³, R⁴, X and n have the meanings indicated, in particular the preferred meanings indicated.
- If L is a reactive esterified OH group, this is preferably alkylsulfonyloxy having 1-6 carbon atoms (preferably methylsulfonyloxy) or arylsulfonyloxy having 6-10 carbon atoms (preferably phenyl- or p-tolylsulfonyloxy, furthermore also 2-naphthalenesulfonyloxy).
- The compounds of the formula I-I can preferably be obtained by a process in which compounds of the formula II-I are reacted with compounds of the formula III.
- If desired, the starting materials can also be formed *in situ* by not isolating them from the reaction mixture, but instead immediately converting them further into the compounds of the formula I-I.
- On the other hand, it is possible to carry out the reaction stepwise.
- The starting compounds of the formulae II-I and III are generally known. If they are not known, they can be prepared by methods known per se. Compounds of the formula II-I can be obtained, for example, by reaction of the corresponding hydroxypyrimidines built up from thiophene derivatives and CN-substituted alkylene carboxylic acid esters with POCl₃ (Eur. J. Med. Chem. 23, 453 (1988)).
- The hydroxypyrimidines are prepared either by dehydrogenation of the corresponding tetrahydrobenzothienopyrimidine compounds or by the cyclisation of 2-aminobenzothiophene-3-carboxylic acid derivatives using

aldehydes or nitriles which is usual for the preparation of pyrimidine derivatives (for example Houben Weyl E9b/2).

In detail, the reaction of the compounds of the formula II-I with the compounds of the formula III is carried out in the presence or absence of an inert solvent at temperatures between about -20 and about 150°, preferably between 20 and 100°.

The addition of an acid-binding agent, for example an alkali or alkaline earth metal hydroxide, carbonate or bicarbonate or another salt of a weak acid of the alkali or alkaline earth metals, preferably of potassium, sodium or calcium, or the addition of an organic base, such as triethylamine, dimethylamine, pyridine or quinoline, or of an excess of the amine component, may be favourable.

Examples of suitable inert solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, di-isopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide, N-methylpyrrolidone or dimethylformamide (DMF); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the said solvents.

It is furthermore possible to convert a radical X in a compound of the formula I-I into another radical X, for example by hydrolysing an ester or a cyano group to give a COOH group.

Ester groups can be saponified, for example, using NaOH or KOH in water, water/THF or water/dioxane at temperatures between 0 and 100°.

Carboxylic acids can be converted into the corresponding carbonyl chlorides, for example using thionyl chloride, and these can be converted

into carboxamides. Elimination of water therefrom in a known manner gives carbonitriles.

An acid of the formula I-I can be converted into the associated acid-addition salt using a base, for example by reaction of equivalent amounts of the acid and the base in an inert solvent, such as ethanol, followed by evaporation. Suitable bases for this reaction are, in particular, those which give physiologically acceptable salts.

Thus, the acid of the formula I-I can be converted into the corresponding metal salt, in particular alkali metal or alkaline earth metal salt, or into the corresponding ammonium salt using a base (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate). Also suitable for this reaction are, in particular, organic bases which give physiologically acceptable salts, such as, for example, ethanolamine.

An acid of the formula I-I can be converted into the associated acid-addition salt using a base, for example by reaction of equivalent amounts of the acid and the base in an inert solvent, such as ethanol, followed by evaporation. Suitable bases for this reaction are, in particular, those which give physiologically acceptable salts.

Thus, the acid of the formula I-I can be converted into the corresponding metal salt, in particular alkali metal or alkaline earth metal salt, or into the corresponding ammonium salt using a base (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate).

Also suitable for this reaction are, in particular, organic bases which give physiologically acceptable salts, such as, for example, ethanolamine.

On the other hand, a base of the formula I-I can be converted into the associated acid-addition salt using an acid, for example by reaction of equivalent amounts of the base and the acid in an inert solvent, such as ethanol, followed by evaporation. Suitable acids for this reaction are, in particular, those which give physiologically acceptable acids. Thus, it is possible to use inorganic acids, for example sulfuric acid, nitric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as orthophosphoric acid, or sulfamic acid, furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or

heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, for example formic acid, acetic acid, propionic acid, pivalic acid, diethyl-acetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenemono- and -disulfonic acids, or laurylsulfuric acid. Salts with physiologically unacceptable acids, for example picrates, can be used for the isolation and/or purification of the compounds of the formula I.

The invention furthermore relates to the pharmaceutical formulations comprising at least one phosphodiesterase V inhibitor of the formula I and/or one of its physiologically acceptable salts and at least one endothelin receptor antagonist and comprising one or more excipients and/or assistants.

The pharmaceutical preparations are prepared, in particular, by non-chemical methods, in which the active ingredients are converted into a suitable dosage form together with at least one solid, liquid and/or semi-liquid excipient or assistant.

These preparations can be used as medicaments in human or veterinary medicine. Suitable excipients are organic or inorganic substances which are suitable for enteral (for example oral), parenteral or topical administration and do no react with the novel compounds, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatine, carbohydrates, such as lactose or starch, magnesium stearates, talc or Vaseline. Suitable for oral administration are, in particular, tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops, suitable for rectal administration are suppositories, suitable for parenteral administration are solutions, preferably oil-based or aqueous solutions, furthermore suspensions, emulsions or implants, and suitable for topical application are ointments, creams or powders. The novel compounds may also be lyophilised and the resultant lyophilisates used, for example, for the preparation of injection preparations. The preparations indicated may be sterilised and/or comprise assistants, such as lubricants,

preservatives, stabilisers and/or wetting agents, emulsifiers, salts for modifying the osmotic pressure, buffer substances, colorants and flavours and/or a plurality of further active ingredients, for example one or more vitamins. They can furthermore be administered as nasal sprays.

5

In general, the substances are preferably administered in doses of between about 1 and 500 mg, in particular between 5 and 100 mg per dosage unit. The daily dose is preferably between about 0.02 and 10 mg/kg of body weight. However, the specific dose for each patient depends on a wide variety of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and method of administration, on the excretion rate, medicament combination and severity of the particular illness to which the therapy applies. Oral administration is preferred.

15

The invention therefore also relates to the use of the pharmaceutical preparations described for the preparation of a medicament for the treatment of angina, high blood pressure, high pulmonary pressure, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cor pulmonale, dextrocardiac insufficiency, atherosclerosis, conditions of reduced patency of the heart vessels, peripheral vascular diseases, strokes, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, irritable bowel syndrome, tumours, renal insufficiency, liver cirrhosis, erectile dysfunction and for the treatment of female sexual disorders.

25

The invention relates, in particular, to the use of the formulations according to the invention for the preparation of a medicament for the treatment of high pulmonary pressure; congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cor pulmonale and/or dextrocardiac insufficiency.

30

The constituents of the novel pharmaceutical [preparation are preferably administered combined. However, they can also be administered individually at the same time or successively.

35

The invention also relates to a set (kit) consisting of separate packs of

- (a) an effective amount of [4-[4-(3-chloro-4-methoxybenzylamino)benzo-thieno[2,3-d]pyrimidin-2-yl]cyclohexane carboxylic acid and/or physiologically acceptable salts and/or solvates thereof

5 and

- (b) an effective amount of a endothelin receptor antagonist.

The set comprises suitable containers, such as boxes, individual bottles, cartons, bags or ampoules. The set may comprise, for example, separate 10 ampoules each containing an effective amount of [4-[4-(3-chloro-4-methoxybenzylamino)benzo-thieno[2,3-d]pyrimidin-2-yl]cyclohexane-carboxylic acid and/or physiologically acceptable salts and/or solvates thereof and of the endothelin receptor antagonist in dissolved or lyophilised form.

15

Above and below, all temperatures are given in °C. In the following examples, "conventional work-up" means that water is added if necessary, the pH is adjusted, if necessary, to between 2 and 10, depending on the constitution of the end product, the mixture is extracted with ethyl acetate or dichloromethane, the phases are separated, the organic phase is dried over sodium sulfate and evaporated, and the product is purified by chromatography on silica gel and/or by crystallisation.

Mass spectrometry (MS): EI (electron impact ionisation) M⁺

25

FAB (fast atom bombardment) (M+H)⁺

Example 1

Methyl 3-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)propionate [obtainable 30 by cyclisation of methyl 2-amino-5,6,7,8-tetrahydrobenzothiophene-3-carboxylate using methyl 3-cyanopropionate, dehydrogenation using sulfur followed by chlorination using phosphorus oxychloride/dimethylamine] and 3-chloro-4-methoxybenzylamine ("A") in N-methylpyrrolidone are stirred at 110° for 5 hours. The solvent is removed, and the mixture is subjected to 35 conventional work-up, giving methyl 3-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]propionate as a colourless oil.

Analogous reaction of "A"

with methyl 2-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)acetate gives

5 methyl 2-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]-
 pyrimidin-2-yl]acetate.

Analogous reaction of 3,4-methylenedioxybenzylamine

10 with methyl 3-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)propionate gives
 methyl 3-[4-(3,4-methylenedioxybenzylamino)benzothieno[2,3-d]-
 pyrimidin-2-yl]propionate.

Analogous reaction of "A"

15 with methyl 4-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)butyrate gives
 methyl 4-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]-
 pyrimidin-2-yl]butyrate.

20 Analogous reaction of 3,4-methylenedioxybenzylamine

with methyl 4-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)butyrate gives
methyl 4-[4-(3,4-methylenedioxybenzylamino)benzothieno[2,3-d]-
pyrimidin-2-yl]butyrate.

25 Analogous reaction of "A"

with methyl 5-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)valerate gives
methyl 5-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]-
pyrimidin-2-yl]valerate.

Analogous reaction of 3,4-methylenedioxybenzylamine

35 with methyl 5-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)valerate gives
 methyl 5-[4-(3,4-methylenedioxybenzylamino)benzothieno[2,3-d]-
 pyrimidin-2-yl]valerate.

Analogous reaction of "A"

with methyl 7-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)heptanoate gives

5 methyl 7-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]-
 pyrimidin-2-yl]heptanoate.

Analogous reaction of 3,4-methylenedioxybenzylamine

10 with methyl 7-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)heptanoate gives
 methyl 7-[4-(3,4-methylenedioxybenzylamino)benzothieno[2,3-d]-
 pyrimidin-2-yl]heptanoate.

Analogous reaction of "A"

15 with methyl 2-[4-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)-cyclohex-1-yl]-
 acetate gives
 methyl 2-{4-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]-
 pyrimidin-2-yl]cyclohexyl-1-yl}acetate.

20 Analogous reaction of 3,4-methylenedioxybenzylamine

with methyl 2-[4-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)-cyclohex-1-yl]-
acetate gives

25 methyl 2-{4-[4-(3,4-methylenedioxybenzylamino)benzothieno[2,3-d]-
 pyrimidin-2-yl]cyclohexyl-1-yl}acetate.

Analogous reaction of benzylamine

30 with methyl 3-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)propionate gives
 methyl 3-(4-benzylamino-benzothieno[2,3-d]pyrimidin-2-yl)propionate;

with methyl 4-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)butyrate gives
 methyl 4-(4-benzylamino-benzothieno[2,3-d]pyrimidin-2-yl)butyrate;

35 with methyl 5-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)valerate gives

methyl 5-(4-benzylamino-benzothieno[2,3-d]pyrimidin-2-yl)valerate.

Analogous reaction of "A"

5 with methyl 4-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)-cyclohexane-carboxylate gives

methyl 4-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]-pyrimidin-2-yl]cyclohexanecarboxylate

10 and reaction of 3,4-methylenedioxybenzylamine gives

methyl 4-[4-(3,4-methylenedioxybenzylamino)benzothieno[2,3-d]-pyrimidin-2-yl]cyclohexanecarboxylate.

Example 2

15

Methyl 3-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]propionate is dissolved in ethylene glycol monomethyl ether, 32%. NaOH is added, and the mixture is stirred at 110° for 5 hours. After 20% HCl has been added, the mixture is extracted with dichloromethane.

20

Addition of petroleum ether gives 3-[4-(3-chloro-4-methoxybenzylamino)-benzothieno[2,3-d]pyrimidin-2-yl]propionic acid, m.p. 218°.

25

The precipitated crystals are dissolved in isopropanol, and ethanolamine is added. Crystallisation gives 3-[4-(3-chloro-4-methoxybenzylamino)benzo-thieno[2,3-d]pyrimidin-2-yl]propionic acid, ethanolamine salt.

The following compounds are obtained analogously:

30

4-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]butyric acid, m.p. 225°; ethanolamine salt, m.p. 150°;

5-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]valeric acid, m.p. 210°; ethanolamine salt, m.p. 141°;

35

4-[4-(3,4-methylenedioxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]butyric acid, hydrochloride, m.p. 245°.

Analogous reaction of the esters listed under Example 1 gives the following carboxylic acids:

- 5 2-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]acetic acid,
- 10 3-[4-(3,4-methylenedioxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]propionic acid,
- 15 5-[4-(3,4-methylenedioxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]valeric acid,
- 20 7-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]heptanoic acid,
- 25 2-[4-[4-(3,4-methylenedioxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]cyclohexyl-1-yl]acetic acid,
- 30 2-[4-[4-(3,4-methylenedioxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]cyclohexyl-1-yl]propionic acid,
- 35 3-(4-benzylamino-benzothieno[2,3-d]pyrimidin-2-yl)propionic acid,
- 4-(4-benzylamino-benzothieno[2,3-d]pyrimidin-2-yl)butyric acid,
- 40 5-(4-benzylamino-benzothieno[2,3-d]pyrimidin-2-yl)valeric acid,
- 45 4-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]cyclohexanecarboxylic acid, ethanolamine salt, m.p. 167°;
- 50 4-[4-(3,4-methylenedioxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]cyclohexanecarboxylic acid, ethanolamine salt, m.p. 143°.

Example 3

5 A mixture of 1.5 g of methyl 4-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)-phenylcarboxylate ("B"), prepared by dehydrogenation of the corresponding 5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine compound using sulfur followed by chlorination using phosphorus oxychloride/dimethylamine, and
10 1.5 g of 3-chloro-4-methoxybenzylamine in 20 ml of N-methylpyrrolidone is heated at 110° for 4 hours. After cooling, the mixture is subjected to conventional work-up, giving 2.6 g of methyl 4-[4-(3-chloro-4-methoxybenzylamino)-[1]-benzothieno[2,3-d]pyrimidin-2-yl]benzoate, m.p. 203-204°.

15 Analogously to Example 2, 1.2 g of the ester give 1.0 g of
4-[4-(3-chloro-4-methoxybenzylamino)-[1]-benzothieno[2,3-d]-pyrimidin-2-yl]benzoic acid, ethanolamine salt, m.p. 189-190°.

20 Analogously to Example 1, "B" and 3,4-methylenedioxybenzylamine give methyl 4-[4-(3,4-methylenedioxybenzylamino)-[1]-benzothieno[2,3-d]-pyrimidin-2-yl]benzoate, and ester hydrolysis thereof gives
4-[4-(3,4-methylenedioxybenzylamino)-[1]-benzothieno[2,3-d]-pyrimidin-2-yl]benzoic acid, sodium salt, m.p. >260°.

The following compounds are obtained analogously:

25 4-[4-(3-chloro-4-methoxybenzylamino)-[1]-benzothieno[2,3-d]-pyrimidin-2-yl]phenylacetic acid, ethanolamine salt, m.p. 130°;
and
4-[4-(3,4-methylenedioxybenzylamino)-[1]-benzothieno[2,3-d]-pyrimidin-2-yl]phenylacetic acid, ethanolamine salt, m.p. 202°.

30 Example 4

1 equivalent of 3-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]-pyrimidin-2-yl]propionic acid and 1.2 equivalents of thionyl chloride are stirred in dichloromethane for 2 hours. The solvent is removed, giving 3-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]-propionyl chloride.

The product is transferred into aqueous ammonia, and the mixture is stirred for one hour and subjected to conventional work-up, giving 3-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]propionamide.

5

Example 5

1 equivalent of DMF and 1 equivalent of oxalyl chloride are dissolved in acetonitrile at 0°. 1 equivalent of 3-[4-(3-chloro-4-methoxybenzylamino)-10 benzothieno[2,3-d]pyrimidin-2-yl]propionamide is then added. The mixture is stirred for a further one hour. Conventional work-up gives 3-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]propionitrile.

Example 6

15

Analogously to Examples 1, 2 and 3, reaction of the corresponding chloropyrimidine derivatives with 3,4-ethylenedioxybenzylamine gives the following carboxylic acids:

20

4-[4-(3,4-ethylenedioxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]butyric acid,

3-[4-(3,4-ethylenedioxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]propionic acid,

25

5-[4-(3,4-ethylenedioxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]valeric acid,

30

7-[4-(3,4-ethylenedioxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]heptanoic acid,

2-[4-[4-(3,4-ethylenedioxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]cyclohexyl-1-yl]acetic acid,

35

4-[4-(3,4-ethylenedioxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]cyclohexanecarboxylic acid,

- 4-[4-(3,4-ethylenedioxybenzylamino)-[1]-benzothieno[2,3-d]pyrimidin-2-yl]benzoic acid, decomp. 220-230°;
- 5 4-[4-(3,4-ethylenedioxybenzylamino)-[1]-benzothieno[2,3-d]pyrimidin-2-yl]benzoic acid, ethanolamine salt, m.p. 252°;
- 10 4-[4-(3,4-ethylenedioxybenzylamino)-[1]-benzothieno[2,3-d]pyrimidin-2-yl]phenylacetic acid.
- 10 Analogous reaction with 3,4-dichlorobenzylamine gives the following compounds:
- 15 4-[4-(3,4-dichlorobenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]-butyric acid,
- 15 3-[4-(3,4-dichlorobenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]-propionic acid,
- 20 5-[4-(3,4-dichlorobenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]-valeric acid, ethanolamine salt, m.p. 160°;
- 25 7-[4-(3,4-dichlorobenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]-heptanoic acid,
- 25 2-[4-[4-(3,4-dichlorobenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]-cyclohexyl-1-yl]acetic acid,
- 30 4-[4-(3,4-dichlorobenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]cyclohexanecarboxylic acid,
- 30 4-[4-(3,4-dichlorobenzylamino)-[1]-benzothieno[2,3-d]pyrimidin-2-yl]benzoic acid,
- 35 4-[4-(3,4-dichlorobenzylamino)-[1]-benzothieno[2,3-d]pyrimidin-2-yl]phenylacetic acid.

Analogous reaction with 3-chloro-4-ethoxybenzylamine gives the following compounds:

5 4-[4-(3-chloro-4-ethoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]butyric acid,

10 3-[4-(3-chloro-4-ethoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]propionic acid,

15 5-[4-(3-chloro-4-ethoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]valeric acid,

20 7-[4-(3-chloro-4-ethoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]heptanoic acid,

25 2-{4-[4-(3-chloro-4-ethoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]cyclohexyl-1-yl}acetic acid,

30 4-[4-(3-chloro-4-ethoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]cyclohexanecarboxylic acid,

35 4-[4-(3-chloro-4-ethoxybenzylamino)-[1]-benzothieno[2,3-d]pyrimidin-2-yl]benzoic acid, m.p. 185-187°;

4-[4-(3-chloro-4-ethoxybenzylamino)-[1]-benzothieno[2,3-d]pyrimidin-2-yl]phenylacetic acid.

Analogous reaction with 3-chloro-4-isopropoxybenzylamine gives the

30 following compounds:

4-[4-(3-chloro-4-isopropoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]butyric acid,

35 3-[4-(3-chloro-4-isopropoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]propionic acid,

- 72 -

5-[4-(3-chloro-4-isopropoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]valeric acid, ethanolamine salt, m.p. 130°;

5 7-[4-(3-chloro-4-isopropoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]heptanoic acid,

10 2-{4-[4-(3-chloro-4-isopropoxybenzylamino)benzothieno[2,3-d]-pyrimidin-2-yl]cyclohexyl-1-yl}acetic acid,

10 4-[4-(3-chloro-4-isopropoxybenzylamino)benzothieno[2,3-d]pyrimidin-2-yl]cyclohexanecarboxylic acid,

15 4-[4-(3-chloro-4-isopropoxybenzylamino)-[1]-benzothieno[2,3-d]-pyrimidin-2-yl]benzoic acid, m.p. 240-241°;

20 4-[4-(3-chloro-4-isopropoxybenzylamino)-[1]-benzothieno[2,3-d]-pyrimidin-2-yl]phenylacetic acid.

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The examples below relate to pharmaceutical preparations:

Example A: Injection vials

5

A solution of 100 g of an active ingredient of the formula I-I, 100 g of the endothelin receptor antagonist and 5 g of disodium hydrogenphosphate in 3 l of bidistilled water is adjusted to pH 6.5 using 2N hydrochloric acid, sterile filtered, transferred into injection vials, lyophilised under sterile conditions and sealed under sterile conditions. Each injection vial contains 5 mg of each active ingredient.

10

Example B: Suppositories

15

A mixture of 20 g of an active ingredient of the formula I-I and 20 g of an endothelin receptor antagonist is melted with 100 g of soya lecithin and 1400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of each active ingredient.

20

Example C: Solution

25

A solution is prepared from 1 g of an active ingredient of the formula I-I, 1 g of an endothelin receptor antagonist, 9.38 g of $\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$, 28.48 g of $\text{Na}_2\text{HPO}_4 \cdot 12 \text{H}_2\text{O}$ and 0.1 g of benzalkonium chloride in 940 ml of bidistilled water. The pH is adjusted to 6.8, and the solution is made up to 1 l and sterilised by irradiation. This solution can be used in the form of eye drops.

Example D: Ointment

30

500 mg of an active ingredient of the formula I-I and 500 mg of an endothelin receptor antagonist are mixed with 99.5 g of Vaseline under aseptic conditions.

35

Example E: Tablets

5 A mixture of 1 kg of active ingredient of the formula I-I, 1 g of an endothelin receptor antagonist, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is pressed in a conventional manner to give tablets in such a way that each tablet contains 10 mg of each active ingredient.

Example F: Coated tablets

10 Tablets are pressed analogously to Example E and subsequently coated in a conventional manner with a coating of sucrose, potato starch, talc, tragacanth and dye.

Example G: Capsules

20 2 kg of active ingredient of the formula I-I and 2 kg of an endothelin receptor antagonist are introduced in a conventional manner into hard gelatine capsules in such a way that each capsule contains 20 mg of each active ingredient.

Example H: Ampoules

25 A solution of 1 kg of active ingredient of the formula I-I and 1 kg of an endothelin receptor antagonist in 60 l of bidistilled water is sterile filtered, transferred into ampoules, lyophilised under sterile conditions and sealed under sterile conditions. Each ampoule contains 10 mg of each active ingredient.

Example I: Inhalation spray

30 35 14 g of active ingredient of the formula I-I and 14 g of an endothelin receptor antagonist are dissolved in 10 l of isotonic NaCl solution, and the solution is transferred into commercially available spray containers with pump mechanism. The solution can be sprayed into the mouth or nose.

- 75 -

One spray shot (about 0.1 ml) corresponds to a dose of about 0.14 mg of each active ingredient.

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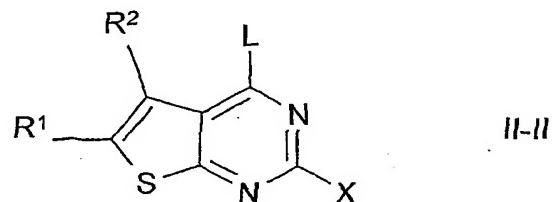
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Compounds of the formula I-II

5 The compounds of the formula I-II according to Claim 1 and their salts are
prepared by a process, characterised in that

a) a compound of the formula II-II

10



in which

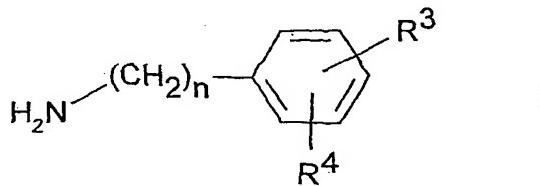
15

R¹, R² and X are as defined above,
and L is Cl, Br, OH, SCH₃ or a reactive esterified OH group,

20

is reacted with a compound of the formula III

25



in which

R³, R⁴ and n are as defined above,

30

or

35

b) a radical X in a compound of the formula I-II is converted into
another radical X by, for example, hydrolysing an ester group to a COOH
group or converting a COOH group into an amide or into a cyano group,

35

and/or in that a compound of the formula I-II is converted into one of its
salts.

The term solvates of the compounds of the formula I-II is taken to mean adductions of inert solvent molecules onto the compounds of the formula I-II which form owing to their mutual attractive forces. Solvates are, for example, mono- or dihydrates or alcoholates.

Above and below, the radicals R¹, R², R³, R⁴, R⁵, R⁶, R⁷, X, L and n are as defined for the formulae I-II, II-II and III, unless expressly stated otherwise.

10 A is alkyl having 1-6 carbon atoms.

In the above formulae, alkyl is preferably unbranched and has 1, 2, 3, 4, 5 or 6 carbon atoms and is preferably methyl, ethyl or propyl, furthermore preferably isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, but also n-pentyl, neopentyl, isopentyl or hexyl.

15

X is an R⁵ or R⁶ radical which is monosubstituted by R⁷.

R⁵ is a linear or branched alkylene radical having 1-10, preferably 1-8, carbon atoms, where the alkylene radical is preferably, for example,

20

methylene, ethylene, propylene, isopropylene, butylene, isobutylene, sec-butylene, pentylene, 1-, 2- or 3-methylbutylene, 1,1-, 1,2- or 2,2-dimethyl-propylene, 1-ethylpropylene, hexylene, 1-, 2-, 3- or 4-methylpentylene, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutylene, 1- or 2-ethylbutylene, 1-ethyl-1-methylpropylene, 1-ethyl-2-methylpropylene, 1,1,2- or 1,2,2-trimethylpropylene, linear or branched heptylene, octylene, nonylene or decylene.

R⁵ is furthermore, for example, but-2-enylene or hex-3-enylene.

R⁶ is cycloalkylalkylene having 6-12 carbon atoms, preferably, for example,

30

cyclopentylmethylen, cyclohexylmethylen, cyclohexylethylen, cyclohexylpropylene or cyclohexylbutylene.

Of the radicals R¹ and R², one is preferably H, while the other is preferably propyl or butyl, but particularly preferably ethyl or methyl. Furthermore, R¹ and R² together are alternatively preferably propylene, butylene or pentylene.

Hal is preferably F, Cl or Br, but alternatively I.

- 5 The radicals R³ and R⁴ may be identical or different and are preferably in
the 3- or 4-position of the phenyl ring. They are, for example, each,
independently of one another, H, OH, alkyl, F, Cl, Br or I or together are
alkylene, such as, for example, propylene, butylene or pentylene, further-
more ethyleneoxy, methylenedioxy or ethylenedioxy. They are alternatively
preferably each alkoxy, such as, for example, methoxy, ethoxy or propoxy.
10
- 10 The radical R⁷ is preferably, for example, COOH, COOCH₃, COOC₂H₅,
CONH₂, CON(CH₃)₂, CONHCH₃ or CN.
- 15 Throughout the invention, all radicals which occur more than once may be
identical or different, i.e. are independent of one another.
- 20 The invention relates, in particular, to pharmaceutical formulations com-
prising an endothelin receptor antagonist and at least one compound of
the formula I-II in which at least one of the said radicals has one of the
preferred meanings indicated above. Some preferred groups of
compounds may be expressed by the following sub-formulae Ia to Ie,
which conform to the formula I-II and in which the radicals not designated
in greater detail are as defined for the formula I-II, but in which
- 25 in Ia X is R⁵ or R⁶, each of which is substituted by COOH or
COOA;
- 30 in Ib R¹ and R² are each, independently of one another, H, A or Hal,
where at least one of the radicals R¹ and R² is always
≠ H,
R³ and R⁴ together are alkylene having 3-5 carbon atoms,
-O-CH₂-CH₂- , -O-CH₂-O- or -O-CH₂-CH₂-O,
X is R⁵ or R⁶, each of which is substituted by COOH or
COOA;

	in Ic	R^1 and R^2	are each, independently of one another, H, A or Hal, where at least one of the radicals R^1 or R^2 is always \neq H,
5		R^3 and R^4	are each, independently of one another, H, A, OA or Hal,
		R^3 and R^4	together are alkylene having 3-5 carbon atoms, -O-CH ₂ -CH ₂ -, -O-CH ₂ -O- or -O-CH ₂ -CH ₂ -O-,
		X	is R^5 or R^6 , each of which is substituted by COOH or COOA,
10		n	is 1 or 2;
	in Id	R^1 and R^2	are each, independently of one another, H, A or Hal, where one of the radicals R^1 and R^2 is always \neq H,
15		R^1 and R^2	together are alternatively alkylene having 3-5 carbon atoms,
		R^3 and R^4	are each, independently of one another, H, A, OA or Hal,
		R^3 and R^4	together are alternatively -O-CH ₂ -O-,
		X	is R^5 which is monosubstituted by R^7 ,
20		R^5	is linear or branched alkylene having 1-10 carbon atoms, or -C ₆ H ₄ -CH ₂ -,
		R^7	is COOH or COOA,
		A	is alkyl having from 1 to 6 carbon atoms,
25		Hal	is F, Cl, Br or I,
		m	is 1, and
		n	is 1 or 2;
	in Ie	R^1 and R^2	are each, independently of one another, H, A or Hal, where one of the radicals R^1 and R^2 is always \neq H,
30		R^1 and R^2	together are alternatively alkylene having 3-5 carbon atoms,
		R^3 and R^4	are each, independently of one another, H, A, OH, OA or Hal,
35		R^3 and R^4	together are alternatively -O-CH ₂ -O-,
		X	is R^5 which is monosubstituted by R^7 ,

- 80 -

- R⁵ is linear or branched alkylene having 1-10 carbon atoms, or -C₆H₄-CH₂-,
- 5 R⁷ is COOH or COOA,
- A is alkyl having from 1 to 6 carbon atoms,
- Hal is F, Cl, Br or I,
- m is 1, and
- n is 1 or 2;
- 10 The invention preferably relates to a formulation comprising 5-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]-pyrimidin-2-yl]valeric acid and physiologically acceptable salts and/or solvates thereof and at least one endothelin receptor antagonist. Besides the free acid, the ethanolamine salt is preferred.
- 15 Preferred endothelin receptor antagonists are those listed above under the PDE V inhibitors of the formula I.
- The phosphodiesterase V inhibitors of the formula I-II and also the starting materials for their preparation are, in addition, prepared by methods known per se, as described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise under reaction conditions which are known and suitable for the said reactions.
- 20 25 Use can also be made here of variants which are known per se, but are not mentioned here in greater detail.
- In the compounds of the formulae II-II or III, R¹, R², R³, R⁴, X and n have the meanings indicated, in particular the preferred meanings indicated.
- 30 If L is a reactive esterified OH group, this is preferably alkylsulfonyloxy having 1-6 carbon atoms (preferably methylsulfonyloxy) or arylsulfonyloxy having 6-10 carbon atoms (preferably phenyl- or p-tolylsulfonyloxy, furthermore also 2-naphthalenesulfonyloxy).
- 35

The compounds of the formula I-II can preferably be obtained by a process in which compounds of the formula II-II are reacted with compounds of the formula III.

- 5 If desired, the starting materials can also be formed in situ by not isolating them from the reaction mixture, but instead immediately converting them further into the compounds of the formula I.
On the other hand, it is possible to carry out the reaction stepwise.
- 10 The starting compounds of the formulae II-II and III are generally known. If they are not known, they can be prepared by methods known per se. Compounds of the formula II-II can be obtained, for example, by reaction of compounds built up from thiophene derivatives and CN-substituted alkylidenecarboxylic acid esters with POCl_3 (Eur. J. Med. Chem. 23, 453
15 (1988)).

In detail, the reaction of the compounds of the formula II-II with the compounds of the formula III is carried out in the presence or absence of an inert solvent at temperatures between about -20 and about 150°, preferably between 20 and 100°.

20 The addition of an acid-binding agent, for example an alkali or alkaline earth metal hydroxide, carbonate or bicarbonate or another salt of a weak acid of the alkali or alkaline earth metals, preferably of potassium, sodium or calcium, or the addition of an organic base, such as triethylamine, dimethylamine, pyridine or quinoline, or of an excess of the amine component, may be favourable.

25 Examples of suitable inert solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, di-isopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as

- acetamide, dimethylacetamide, N-methylpyrrolidone or dimethylformamide (DMF); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the said solvents.
- 5 It is furthermore possible to convert a radical X in a compound of the formula I-II into another radical X, for example by hydrolysing an ester or a cyano group to give a COOH group.
- 10 Ester groups can be saponified, for example, using NaOH or KOH in water, water/THF or water/dioxane at temperatures between 0 and 100°. Carboxylic acids can be converted into the corresponding carbonyl chlorides, for example using thionyl chloride, and these can be converted into carboxamides. Elimination of water therefrom in a known manner gives carbonitriles.
- 15 An acid of the formula I-II can be converted into the associated acid-addition salt using a base, for example by reaction of equivalent amounts of the acid and the base in an inert solvent, such as ethanol, followed by evaporation. Suitable bases for this reaction are, in particular, those which give physiologically acceptable salts.
- 20 Thus, the acid of the formula I-II can be converted into the corresponding metal salt, in particular alkali metal or alkaline earth metal salt, or into the corresponding ammonium salt using a base (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate).
- 25 Also suitable for this reaction are, in particular, organic bases which give physiologically acceptable salts, such as, for example, ethanolamine.
- 30 An acid of the formula I-II can be converted into the associated acid-addition salt using a base, for example by reaction of equivalent amounts of the acid and the base in an inert solvent, such as ethanol, followed by evaporation. Suitable bases for this reaction are, in particular, those which give physiologically acceptable salts.
- 35 Thus, the acid of the formula I-II can be converted into the corresponding metal salt, in particular alkali metal or alkaline earth metal salt, or into the corresponding ammonium salt using a base (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate).

Also suitable for this reaction are, in particular, organic bases which give physiologically acceptable salts, such as, for example, ethanolamine.

On the other hand, a base of the formula I-II can be converted into the
5 associated acid-addition salt using an acid, for example by reaction of equivalent amounts of the base and the acid in an inert solvent, such as ethanol, followed by evaporation. Suitable acids for this reaction are, in particular, those which give physiologically acceptable acids. Thus, it is possible to use inorganic acids, for example sulfuric acid, nitric acid,
10 hydrohalic acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as orthophosphoric acid, or sulfamic acid, furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, for example formic acid, acetic acid, propionic acid, pivalic acid, diethyl-
15 acetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenemono- and -disulfonic acids, or
20 laurylsulfuric acid. Salts with physiologically unacceptable acids, for example picrates, can be used for the isolation and/or purification of the compounds of the formula I.

The invention furthermore relates to the pharmaceutical formulations
25 comprising at least one phosphodiesterase V inhibitor of the formula I-II and/or one of its physiologically acceptable salts and at least one endothelin receptor antagonist and comprising one or more excipients and/or assistants.

The pharmaceutical preparations are prepared, in particular, by non-
30 chemical methods, in which the active ingredients are converted into a suitable dosage form together with at least one solid, liquid and/or semi-liquid excipient or assistant.

These preparations can be used as medicaments in human or veterinary
35 medicine. Suitable excipients are organic or inorganic substances which are suitable for enteral (for example oral), parenteral or topical administra-

tion and do no react with the novel compounds, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatine, carbohydrates, such as lactose or starch, magnesium stearates, talc or Vaseline. Suitable for oral administration are, in particular, tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops, suitable for rectal administration are suppositories; suitable for parenteral administration are solutions, preferably oil-based or aqueous solutions, furthermore suspensions, emulsions or implants, and suitable for topical application are ointments, creams or powders. The novel compounds may also be lyophilised and the resultant lyophilisates used, for example, for the preparation of injection preparations. The preparations indicated may be sterilised and/or comprise assistants, such as lubricants, preservatives, stabilisers and/or wetting agents, emulsifiers, salts for modifying the osmotic pressure, buffer substances, colorants and flavours and/or a plurality of further active ingredients, for example one or more vitamins. They can furthermore be administered as nasal sprays.

In general, the substances are preferably administered in doses of between about 1 and 500 mg, in particular between 5 and 100 mg per dosage-unit. The daily dose is preferably between about 0.02 and 10 mg/kg of body weight. However, the specific dose for each patient depends on a wide variety of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and method of administration, on the excretion rate, medicament combination and severity of the particular illness to which the therapy applies. Oral administration is preferred.

The invention therefore also relates to the use of the pharmaceutical preparations described for the preparation of a medicament for the treatment of angina, high blood pressure, high pulmonary pressure, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cor pulmonale, dextrocardiac insufficiency, atherosclerosis, conditions of reduced patency of the heart vessels, peripheral vascular diseases, strokes, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, irritable bowel syndrome, tumours, renal insufficiency, liver

cirrhosis, erectile dysfunction and for the treatment of female sexual disorders.

5 The invention relates, in particular, to the use of the formulations according to the invention for the preparation of a medicament for the treatment of high pulmonary pressure, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cor pulmonale and/or dextrocardiac insufficiency.

10 The constituents of the novel pharmaceutical [preparation are preferably administered combined. However, they can also be administered individually at the same time or successively.

15 The invention also relates to a set (kit) consisting of separate packs of
(a) an effective amount of 5-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl]valeric acid and/or physiologically acceptable salts and/or solvates thereof and
(b) an effective amount of an endothelin receptor antagonist.

20 The set comprises suitable containers, such as boxes, individual bottles, cartons, bags or ampoules. The set may comprise, for example, separate ampoules each containing an effective amount of 5-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl]valeric acid and/or physiologically acceptable salts and/or solvates thereof and of the endothelin receptor antagonist in dissolved or lyophilised form.

30 Above and below, all temperatures are given in °C. In the following examples, "conventional work-up" means that water is added if necessary, the pH is adjusted, if necessary, to between 2 and 10, depending on the constitution of the end product, the mixture is extracted with ethyl acetate or dichloromethane, the phases are separated, the organic phase is dried over sodium sulfate and evaporated, and the product is purified by chromatography on silica gel and/or by crystallisation.

Mass spectrometry (MS); EI (electron impact ionisation) M⁺
FAB (fast atom bombardment) (M+H)⁺

Example 1

5

1.9 g of methyl 3-(4-chloro-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]-pyrimidin-2-yl)propionate [obtainable by cyclisation of methyl 2-amino-4,5,6,7-tetrahydrobenzothiophene-3-carboxylate using methyl 3-cyano-propionate followed by chlorination using phosphorus oxychloride/dimethylamine] and 2.3 g of 3-chloro-4-methoxybenzylamine ("A") in 20 ml of N-methylpyrrolidone are stirred at 110° for 5 hours. The solvent is removed, and the product is subjected to conventional work-up, giving 2.6 g of methyl 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl]propionate as a colourless oil.

15

Analogous reaction of "A"

with methyl 3-(4-chloro-5,6-cyclopenteno-[1]-benzothieno[2,3-d]pyrimidin-2-yl)propionate gives

20

methyl 3-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclopenteno-[1]-benzothieno[2,3-d]pyrimidin-2-yl]propionate;

with methyl 3-(4-chloro-5,6-cyclohepteno-[1]-benzothieno[2,3-d]pyrimidin-2-yl)propionate gives

25

methyl 3-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclohepteno-[1]-benzothieno[2,3-d]pyrimidin-2-yl]propionate;

with methyl 3-(4-chloro-6-methylthieno[2,3-d]pyrimidin-2-yl)propionate gives

30

methyl 3-[4-(3-chloro-4-methoxybenzylamino)-6-methylthieno[2,3-d]-pyrimidin-2-yl]propionate;

with methyl 3-(4-chloro-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl)propionate gives

35

methyl 3-[4-(3-chloro-4-methoxybenzylamino)-5,6-dimethylthieno-[2,3-d]pyrimidin-2-yl]propionate;

with methyl 3-(4-chloro-6-ethylthieno[2,3-d]pyrimidin-2-yl)propionate gives
methyl 3-[4-(3-chloro-4-methoxybenzylamino)-6-ethylthieno[2,3-d]-
pyrimidin-2-yl]propionate;

5

with methyl 3-(4,6-dichlorothieno[2,3-d]pyrimidin-2-yl)propionate gives
methyl 3-[4-(3-chloro-4-methoxybenzylamino)-6-chlorothieno[2,3-d]-
pyrimidin-2-yl]propionate;

10

with methyl 2-(4-chloro-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-
2-yl)-acetate gives
methyl 2-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-
benzothieno[2,3-d]pyrimidin-2-yl]acetate.

15

Analogous reaction of 3,4-methylenedioxybenzylamine

with methyl 3-(4-chloro-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-
2-yl)propionate gives

20

methyl 3-[4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro-[1]-
benzothieno[2,3-d]pyrimidin-2-yl]propionate;

with methyl 3-(4-chloro-5,6-cyclopenteno-[1]-benzothieno[2,3-d]pyrimidin-
2-yl)propionate gives

25

methyl 3-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclopenteno-[1]-
benzothieno[2,3-d]pyrimidin-2-yl]propionate;

with methyl 3-(4-chloro-5,6-cyclohepteno-[1]-benzothieno[2,3-d]pyrimidin-
2-yl)propionate gives

30

methyl 3-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclohepteno-[1]-
benzothieno[2,3-d]pyrimidin-2-yl]propionate;

with methyl 3-(4-chloro-6-methylthieno[2,3-d]pyrimidin-2-yl)propionate
gives

35

methyl 3-[4-(3,4-methylenedioxybenzylamino)-6-methylthieno[2,3-d]-
pyrimidin-2-yl]propionate;

with methyl 3-(4-chloro-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl)propionate gives

methyl 3-[4-(3,4-methylenedioxybenzylamino)-5,6-dimethylthieno-[2,3-d]pyrimidin-2-yl]propionate;

5

with methyl 3-(4-chloro-6-ethylthieno[2,3-d]pyrimidin-2-yl)propionate gives

methyl 3-[4-(3,4-methylenedioxybenzylamino)-6-ethylthieno[2,3-d]-pyrimidin-2-yl]propionate;

10

with methyl 3-(4,6-dichlorothieno[2,3-d]pyrimidin-2-yl)propionate gives

methyl 3-[4-(3,4-methylenedioxybenzylamino)-6-chlorothieno[2,3-d]-pyrimidin-2-yl]propionate.

15

Analogous reaction of "A"

15

with methyl 4-(4-chloro-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl)butyrate gives

methyl 4-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl]butyrate;

20

with methyl 4-(4-chloro-5,6-cyclopenteno-[1]-benzothieno[2,3-d]pyrimidin-2-yl)butyrate gives

methyl 4-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclopenteno-[1]-benzothieno[2,3-d]pyrimidin-2-yl]butyrate;

25

with methyl 4-(4-chloro-5,6-cyclohepteno-[1]-benzothieno[2,3-d]pyrimidin-2-yl)butyrate gives

methyl 4-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclohepteno-[1]-benzothieno[2,3-d]pyrimidin-2-yl]butyrate;

30

with methyl 4-(4-chloro-6-methylthieno[2,3-d]pyrimidin-2-yl)butyrate gives

methyl 4-[4-(3-chloro-4-methoxybenzylamino)-6-methylthieno[2,3-d]-pyrimidin-2-yl]butyrate;

35

with methyl 4-(4-chloro-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl)butyrate

gives

- 89 -

methyl 4-[4-(3-chloro-4-methoxybenzylamino)-5,6-dimethylthieno-[2,3-d]pyrimidin-2-yl]butyrate;

- with methyl 4-(4-chloro-6-ethylthieno[2,3-d]pyrimidin-2-yl)butyrate gives
5 methyl 4-[4-(3-chloro-4-methoxybenzylamino)-6-ethylthieno[2,3-d]-
 pyrimidin-2-yl]butyrate;
- with methyl 4-(4,6-chloro-6-chlorothieno[2,3-d]pyrimidin-2-yl)butyrate gives
10 methyl 4-[4-(3-chloro-4-methoxybenzylamino)-6-chlorothieno[2,3-d]-
 pyrimidin-2-yl]butyrate.

Analogous reaction of 3,4-methylenedioxybenzylamine

- with methyl 4-(4-chloro-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-
15 2-yl)butyrate gives
 methyl 4-[4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro-[1]-
 benzothieno[2,3-d]pyrimidin-2-yl]butyrate;
- with methyl 4-(4-chloro-5,6-cyclopenteno-[1]-benzothieno[2,3-d]pyrimidin-
20 2-yl)butyrate gives
 methyl 4-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclopenteno-[1]-
 benzothieno[2,3-d]pyrimidin-2-yl]butyrate;
- with methyl 4-(4-chloro-5,6-cyclohepteno-[1]-benzothieno[2,3-d]pyrimidin-
25 2-yl)butyrate gives
 methyl 4-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclohepteno-[1]-
 benzothieno[2,3-d]pyrimidin-2-yl]butyrate;
- with methyl 4-(4-chloro-6-methylthieno[2,3-d]pyrimidin-2-yl)butyrate gives
30 methyl 4-[4-(3,4-methylenedioxybenzylamino)-6-methylthieno[2,3-d]-
 pyrimidin-2-yl]butyrate;
- with methyl 4-(4-chloro-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl)butyrate
gives
35 methyl 4-[4-(3,4-methylenedioxybenzylamino)-5,6-dimethylthieno-[2,3-d]pyrimidin-2-yl]butyrate;

- 90 -

with methyl 4-(4-chloro-6-ethylthieno[2,3-d]pyrimidin-2-yl)butyrate gives
methyl 4-[4-(3,4-methylenedioxybenzylamino)-6-ethylthieno[2,3-d]-
pyrimidin-2-yl]butyrate;

5

with methyl 4-(4,6-dichlorothieno[2,3-d]pyrimidin-2-yl)butyrate gives
methyl 4-[4-(3,4-methylenedioxybenzylamino)-6-chlorothieno[2,3-d]-
pyrimidin-2-yl]butyrate.

10 Analogous reaction of "A"

with methyl 5-(4-chloro-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-
2-yl)valerate gives

15 methyl 5-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-
benzothieno[2,3-d]pyrimidin-2-yl]valerate;

with methyl 5-(4-chloro-5,6-cyclopenteno-[1]-benzothieno[2,3-d]pyrimidin-
2-yl)valerate gives

20 methyl 5-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclopenteno-[1]-
benzothieno[2,3-d]pyrimidin-2-yl]valerate;

with methyl 5-(4-chloro-5,6-cyclohepteno-[1]-benzothieno[2,3-d]pyrimidin-
2-yl)- valerate gives

25 methyl 5-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclohepteno-[1]-
benzothieno[2,3-d]pyrimidin-2-yl]valerate;

with methyl 5-(4-chloro-6-methylthieno[2,3-d]pyrimidin-2-yl)valerate gives
methyl 5-[4-(3-chloro-4-methoxybenzylamino)-6-methylthieno[2,3-d]-
pyrimidin-2-yl]valerate;

30

with methyl 5-(4-chloro-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl)valerate
gives

methyl 5-[4-(3-chloro-4-methoxybenzylamino)-5,6-dimethylthieno-[2,3-d]-
pyrimidin-2-yl]valerate;

35

with methyl 5-(4-chloro-6-ethylthieno[2,3-d]pyrimidin-2-yl)valerate gives

- 91 -

methyl 5-[4-(3-chloro-4-methoxybenzylamino)-6-ethylthieno[2,3-d]-pyrimidin-2-yl]valerate;

with methyl 5-(4,6-dichlorothieno[2,3-d]pyrimidin-2-yl)valerate gives

5 methyl 5-[4-(3-chloro-4-methoxybenzylamino)-6-chlorothieno[2,3-d]-pyrimidin-2-yl]valerate.

Analogous reaction of 3,4-methylenedioxybenzylamine

10 with methyl 5-(4-chloro-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl)valerate gives

 methyl 5-[4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl]valerate;

15 with methyl 5-(4-chloro-5,6-cyclopenteno-[1]-benzothieno[2,3-d]pyrimidin-2-yl)valerate gives

 methyl 5-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclopenteno-[1]-benzothieno[2,3-d]pyrimidin-2-yl]valerate;

20 with methyl 5-(4-chloro-5,6-cyclohepteno-[1]-benzothieno[2,3-d]pyrimidin-2-yl)valerate gives

 methyl 5-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclohepteno-[1]-benzothieno[2,3-d]pyrimidin-2-yl]valerate;

25 with methyl 5-(4-chloro-6-methylthieno[2,3-d]pyrimidin-2-yl)valerate gives

 methyl 5-[4-(3,4-methylenedioxybenzylamino)-6-methylthieno[2,3-d]-

 pyrimidin-2-yl]valerate;

with methyl 5-(4-chloro-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl)valerate

30 gives

 methyl 5-[4-(3,4-methylenedioxybenzylamino)-5,6-dimethylthieno-[2,3-d]pyrimidin-2-yl]valerate;

with methyl 5-(4-chloro-6-ethylthieno[2,3-d]pyrimidin-2-yl)valerate gives

35 methyl 5-[4-(3,4-methylenedioxybenzylamino)-6-ethylthieno[2,3-d]-pyrimidin-2-yl]valerate;

- 92 -

with methyl 5-(4,6-dichlorothieno[2,3-d]pyrimidin-2-yl)valerate gives
methyl 5-[4-(3,4-methylenedioxybenzylamino)-6-chlorothieno[2,3-d]-
pyrimidin-2-yl]valerate.

5

Analogous reaction of "A"

with methyl 7-(4-chloro-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-
2-yl)heptanoate gives

10

methyl 7-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-
benzothieno[2,3-d]pyrimidin-2-yl]heptanoate;

with methyl 7-(4-chloro-5,6-cyclopenteno-[1]-benzothieno[2,3-d]pyrimidin-
2-yl)heptanoate gives

15

methyl 7-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclopenteno-[1]-
benzothieno[2,3-d]pyrimidin-2-yl]heptanoate;

with methyl 7-(4-chloro-5,6-cyclohepteno-[1]-benzothieno[2,3-d]pyrimidin-
2-yl)heptanoate gives

20

methyl 7-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclohepteno-[1]-
benzothieno[2,3-d]pyrimidin-2-yl]heptanoate;

with methyl 7-(4-chloro-6-methylthieno[2,3-d]pyrimidin-2-yl)heptanoate
gives

25

methyl 7-[4-(3-chloro-4-methoxybenzylamino)-6-methylthieno[2,3-d]-
pyrimidin-2-yl]heptanoate;

with methyl 7-(4-chloro-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl)heptanoate
gives

30

methyl 7-[4-(3-chloro-4-methoxybenzylamino)-5,6-dimethylthieno-[2,3-d]-
pyrimidin-2-yl]heptanoate;

with methyl 7-(4-chloro-6-ethylthieno[2,3-d]pyrimidin-2-yl)heptanoate gives
methyl 7-[4-(3-chloro-4-methoxybenzylamino)-6-ethylthieno[2,3-d]-
pyrimidin-2-yl]heptanoate;

35

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with methyl 7-(4-chloro-6-chlorothieno[2,3-d]pyrimidin-2-yl)heptanoate gives

methyl 7-[4-(3-chloro-4-methoxybenzylamino)-6-chlorothieno[2,3-d]-pyrimidin-2-yl]heptanoate.

5

Analogous reaction of 3,4-methylenedioxybenzylamine

with methyl 7-(4-chloro-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl)heptanoate gives

10

methyl 7-[4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl]heptanoate;

with methyl 7-(4-chloro-5,6-cyclopenteno-[1]-benzothieno[2,3-d]pyrimidin-2-yl)heptanoate gives

15

methyl 7-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclopenteno-[1]-benzothieno[2,3-d]pyrimidin-2-yl]heptanoate;

with methyl 7-(4-chloro-5,6-cyclohepteno-[1]-benzothieno[2,3-d]pyrimidin-2-yl)heptanoate gives

20

methyl 7-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclohepteno-[1]-benzothieno[2,3-d]pyrimidin-2-yl]heptanoate;

with methyl 7-(4-chloro-6-methylthieno[2,3-d]pyrimidin-2-yl)heptanoate gives

25

methyl 7-[4-(3,4-methylenedioxybenzylamino)-6-methylthieno[2,3-d]-pyrimidin-2-yl]valerate;

with methyl 7-(4-chloro-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl)heptanoate gives

30

methyl 7-[4-(3,4-methylenedioxybenzylamino)-5,6-dimethylthieno-[2,3-d]pyrimidin-2-yl]heptanoate;

with methyl 7-(4-chloro-6-ethylthieno[2,3-d]pyrimidin-2-yl)heptanoate gives
methyl 7-[4-(3,4-methylenedioxybenzylamino)-6-ethylthieno[2,3-d]-pyrimidin-2-yl]heptanoate;

35

with methyl 7-(4,6-dichlorothieno[2,3-d]pyrimidin-2-yl)heptanoate gives
methyl 7-[4-(3,4-methylenedioxybenzylamino)-6-chlorothieno[2,3-d]-
pyrimidin-2-yl]heptanoate.

5 Analogous reaction of "A"

- with methyl 2-[4-(4-chloro-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]-
pyrimidin-2-yl)-cyclohexyl-1-yl]acetate gives
methyl 2-{4-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-
10 [1]-benzothieno[2,3-d]pyrimidin-2-yl]cyclohexyl-1-yl}acetate;
- with methyl 2-[4-(4-chloro-6-ethylthieno[2,3-d]pyrimidin-2-yl)-cyclohexyl-1-
yl]acetate gives
methyl 2-{4-[4-(3-chloro-4-methoxybenzylamino)-6-ethylthieno[2,3-d]-
15 pyrimidin-2-yl]cyclohexyl-1-yl}acetate;

Analogous reaction of 3,4-methylenedioxybenzylamine

- 20 with methyl 2-[4-(4-chloro-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]-
pyrimidin-2-yl)-cyclohexyl-1-yl]acetate gives
methyl 2-{4-[4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro-
[1]-benzothieno[2,3-d]pyrimidin-2-yl]cyclohexyl-1-yl}acetate.

Analogous reaction of benzylamine

- 25 with methyl 3-(4-chloro-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-
2-yl)propionate gives
methyl 3-(4-benzylamino-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]-
30 pyrimidin-2-yl)propionate;
- with methyl 4-(4-chloro-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-
2-yl)butyrate gives
methyl 4-(4-benzylamino-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]-
35 pyrimidin-2-yl)butyrate;

- 95 -

with methyl 5-(4-chloro-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl)valerate gives

methyl 5-(4-benzylamino-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl)valerate;

5

with methyl 4-(4-chloro-6-methylthieno[2,3-d]pyrimidin-2-yl)butyrate gives

methyl 4-[4-benzylamino-6-methylthieno[2,3-d]pyrimidin-2-yl]butyrate;

with methyl 5-(4-chloro-6-ethylthieno[2,3-d]pyrimidin-2-yl)valerate gives

10

methyl 5-[4-benzylamino-6-ethylthieno[2,3-d]pyrimidin-2-yl]valerate.

Example 2

2.2 g of methyl 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-

15

[1]-benzothieno[2,3-d]pyrimidin-2-yl]propionate are dissolved in 20 ml of ethylene glycol monomethyl ether, 10 ml of 32% NaOH are added, and the mixture is stirred at 110° for 5 hours. After 20% HCl has been added, the mixture is extracted with dichloromethane. Addition of petroleum ether gives 2.0 g of 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl]propionic acid, m.p. 229°.

20

The precipitated crystals are dissolved in 30 ml of isopropanol, and 0.5 g of ethanolamine is added. Crystallisation gives 1.3 g of 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl]propionic acid, ethanolamine salt, m.p. 135°.

25

Analogous reaction of the esters listed under Example 1 gives the following carboxylic acids:

3-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclopenteno-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl]propionic acid;

30

3-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclohepteno-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl]propionic acid;

35

3-[4-(3-chloro-4-methoxybenzylamino)-6-methylthieno[2,3-d]pyrimidin-2-yl]propionic acid;

- 3-[4-(3-chloro-4-methoxybenzylamino)-5,6-methylthieno[2,3-d]-pyrimidin-2-yl]propionic acid;
- 5 3-[4-(3-chloro-4-methoxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]propionic acid;
- 10 3-[4-(3-chloro-4-methoxybenzylamino)-6-chlorothieno[2,3-d]pyrimidin-2-yl]propionic acid;
- 15 2-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl]acetic acid, ethanolamine salt, m.p. 126°;
- 20 3-[4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl]propionic acid;
- 25 3-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclopenteno-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl]propionic acid;
- 30 3-[4-(3,4-methylenedioxybenzylamino)-6-methylthieno[2,3-d]-pyrimidin-2-yl]propionic acid;
- 35 3-[4-(3,4-methylenedioxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]propionic acid;
- 4-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl]butyric acid;

- 4-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclopenteno-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl]butyric acid;
- 5 4-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclohepteno-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl]butyric acid;
- 10 4-[4-(3-chloro-4-methoxybenzylamino)-6-methylthieno[2,3-d]-pyrimidin-2-yl]butyric acid, ethanolamine salt, m.p. 142°;
- 15 4-[4-(3-chloro-4-methoxybenzylamino)-5,6-methylthieno[2,3-d]-pyrimidin-2-yl]butyric acid;
- 20 4-[4-(3-chloro-4-methoxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]butyric acid, ethanolamine salt, m.p. 170°;
- 25 4-[4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl]butyric acid, ethanolamine salt, m.p. 114°;
- 30 4-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclopenteno-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl]butyric acid;
- 35 4-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclohepteno-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl]butyric acid;
- 40 4-[4-(3,4-methylenedioxybenzylamino)-6-methylthieno[2,3-d]-pyrimidin-2-yl]butyric acid, ethanolamine salt, m.p. 170°;
- 45 4-[4-(3,4-methylenedioxybenzylamino)-5,6-dimethylthieno[2,3-d]-pyrimidin-2-yl]butyric acid;
- 50 4-[4-(3,4-methylenedioxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]butyric acid;

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- 4-[4-(3,4-methylenedioxybenzylamino)-6-chlorothieno[2,3-d]pyrimidin-2-yl]butyric acid;
- 5 5-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl]valeric acid, m.p. 165°; ethanolamine salt, m.p. 112°;
- 10 5-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclopenteno-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl]valeric acid;
- 15 5-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclohepteno-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl]valeric acid;
- 20 5-[4-(3-chloro-4-methoxybenzylamino)-6-methylthieno[2,3-d]-pyrimidin-2-yl]valeric acid, ethanolamine salt, m.p. 156°;
- 25 5-[4-(3-chloro-4-methoxybenzylamino)-5,6-dimethylthieno[2,3-d]-pyrimidin-2-yl]valeric acid;
- 30 5-[4-(3-chloro-4-methoxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]valeric acid, ethanolamine salt, m.p. 156°;
- 35 5-[4-(3-chloro-4-methoxybenzylamino)-6-chlorothieno[2,3-d]pyrimidin-2-yl]valeric acid;
- 5-[4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl]valeric acid;
- 5-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclopenteno-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl]valeric acid;

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- 5-[4-(3,4-methylenedioxybenzylamino)-6-methylthieno[2,3-d]-pyrimidin-2-yl]valeric acid, ethanolamine salt, m.p. 167°;
- 5 5-[4-(3,4-methylenedioxybenzylamino)-5,6-dimethylthieno[2,3-d]-pyrimidin-2-yl]valeric acid;
- 10 5-[4-(3,4-methylenedioxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]valeric acid;
- 15 7-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl]heptanoic acid, ethanolamine salt, m.p. 130°;
- 20 7-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclopenteno-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl]heptanoic acid;
- 25 7-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclohepteno-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl]heptanoic acid;
- 30 7-[4-(3-chloro-4-methoxybenzylamino)-6-methylthieno[2,3-d]-pyrimidin-2-yl]heptanoic acid;
- 35 7-[4-(3-chloro-4-methoxybenzylamino)-5,6-dimethylthieno[2,3-d]-pyrimidin-2-yl]heptanoic acid;
- 35 7-[4-(3-chloro-4-methoxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]heptanoic acid;

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- 7-[4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl]heptanoic acid, ethanolamine salt, m.p. 137°;
- 5 7-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclopenteno-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl]heptanoic acid;
- 10 7-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclohepteno-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl]heptanoic acid;
- 15 7-[4-(3,4-methylenedioxybenzylamino)-6-methylthieno[2,3-d]-pyrimidin-2-yl]valeric acid;
- 20 7-[4-(3,4-methylenedioxybenzylamino)-5,6-dimethylthieno[2,3-d]-pyrimidin-2-yl]heptanoic acid;
- 25 7-[4-(3,4-methylenedioxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]heptanoic acid;
- 30 2-{4-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl]cyclohexyl}acetic acid;
- 35 2-{4-[4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl]cyclohexyl}acetic acid;
- 3-(4-benzylamino-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl)propionic acid, ethanolamine salt, m.p. 126°;
- 4-(4-benzylamino-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl)butyric acid, ethanolamine salt, m.p. 133°;

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5-(4-benzylamino-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl)valeric acid, ethanolamine salt, m.p. 135°;

5 4-[4-benzylamino-6-methylthieno[2,3-d]pyrimidin-2-yl]butyric acid, ethanolamine salt, m.p. 165°;

5-[4-benzylamino-6-ethylthieno[2,3-d]pyrimidin-2-yl]valeric acid, ethanolamine salt, m.p. 162°.

10

Example 3

15 1 equivalent of 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl]propionic acid and 1.2 equivalents of thionyl chloride are stirred in dichloromethane for 2 hours. The solvent is removed, giving 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl]propionyl chloride. The product is transferred into aqueous ammonia, and the mixture is stirred for one hour and subjected to conventional work-up, giving 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]-20 pyrimidin-2-yl]propionamide.

Example 4

25 1 equivalent of DMF and 1 equivalent of oxalyl chloride are dissolved in acetonitrile at 0°. 1 equivalent of 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl]propionamide is then added. The mixture is stirred for a further one hour. Conventional work-up gives 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl]propionitrile.

Example 5

The following compounds are obtained analogously to Examples 1 and 2:

35

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- 6-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]pyrimidin-2-yl]hexanoic acid, m.p. 165°;
- 5 2-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]pyrimidin-2-yl]propionic acid, ethanolamine salt, m.p. 150°;
- 10 4-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]pyrimidin-2-yl]2,2-dimethylbutyric acid, ethanolamine salt, m.p. 130°;
- 15 5-[4-(3-chloro-4-hydroxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]pyrimidin-2-yl]valeric acid, m.p. 179°;
- 20 5-[4-(3,4-dichlorobenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]-pyrimidin-2-yl]valeric acid, ethanolamine salt ,m.p. 136°;
- 25 5-[4-(3-chloro-4-isopropoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl]valeric acid, ethanolamine salt, m.p. 118°;
- 2-[4-(4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl)-phenyl]acetic acid, ethanolamine salt,
m.p. 119°;
- 30 2-[4-(4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzo-thieno[2,3-d]pyrimidin-2-yl)-phenyl]acetic acid, m.p. 214°.

The examples below relate to pharmaceutical preparations:

Example A: Injection vials

5

A solution of 100 g of an active ingredient of the formula I-II, 100 g of the endothelin receptor antagonist and 5 g of disodium hydrogenphosphate in 3 l of bidistilled water is adjusted to pH 6.5 using 2N hydrochloric acid, sterile filtered, transferred into injection vials, lyophilised under sterile conditions and sealed under sterile conditions. Each injection vial contains 5 mg of each active ingredient.

10

Example B: Suppositories

15

A mixture of 20 g of an active ingredient of the formula I-II and 20 g of an endothelin receptor antagonist is melted with 100 g of soya lecithin and 1400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of each active ingredient.

20

Example C: Solution

A solution is prepared from 1 g of an active ingredient of the formula I-II, 1 g of an endothelin receptor antagonist, 9.38 g of $\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$, 28.48 g of $\text{Na}_2\text{HPO}_4 \cdot 12 \text{H}_2\text{O}$ and 0.1 g of benzalkonium chloride in 940 ml of

25

bidistilled water. The pH is adjusted to 6.8, and the solution is made up to 1 l and sterilised by irradiation. This solution can be used in the form of eye drops.

Example D: Ointment

30

500 mg of an active ingredient of the formula I-II and 500 mg of an endothelin receptor antagonist are mixed with 99.5 g of Vaseline under aseptic conditions.

35

Example E: Tablets

5 A mixture of 1 kg of active ingredient of the formula I-II, 1 g of an endothelin receptor antagonist, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is pressed in a conventional manner to give tablets in such a way that each tablet contains 10 mg of each active ingredient.

Example F: Coated tablets

10 Tablets are pressed analogously to Example E and subsequently coated in a conventional manner with a coating of sucrose, potato starch, talc, tragacanth and dye.

Example G: Capsules

15 2 kg of active ingredient of the formula I-II and 2 kg of an endothelin receptor antagonist are introduced in a conventional manner into hard gelatine capsules in such a way that each capsule contains 20 mg of each active ingredient.

20 **Example H: Ampoules**

A solution of 1 kg of active ingredient of the formula I-II and 1 kg of an endothelin receptor antagonist in 60 l of bidistilled water is sterile filtered, transferred into ampoules, lyophilised under sterile conditions and sealed under sterile conditions. Each ampoule contains 10 mg of each active ingredient.

Example I: Inhalation spray

30 14 g of active ingredient of the formula I-II and 14 g of an endothelin receptor antagonist are dissolved in 10 l of isotonic NaCl solution, and the solution is transferred into commercially available spray containers with pump mechanism. The solution can be sprayed into the mouth or nose. One spray shot (about 0.1 ml) corresponds to a dose of about 0.14 mg of each active ingredient.

Patent Claims

1. Pharmaceutical formulation comprising at least one compound of the formula I

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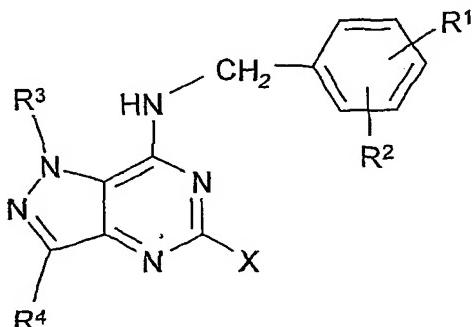
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30

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in which

R¹ and R² are each, independently of one another, H, A, OH, OA or Hal,

R¹ and R² together are alternatively alkylene having 3-5 carbon atoms, -O-CH₂-CH₂-, -CH₂-O-CH₂-, -O-CH₂-O- or -O-CH₂-CH₂-O-,

R³ and R⁴ are each, independently of one another, H or A,

X is R⁵, R⁶ or R⁷, each of which is monosubstituted by R⁸,

R⁵ is linear or branched alkylene having 1-10 carbon atoms, in which one or two CH₂ groups may be replaced by -CH=CH- groups, O, S or SO,

R⁶ is cycloalkyl or cycloalkylalkylene having 5-12 carbon atoms,

R⁷ is phenyl or phenylmethyl,

R⁸ is COOH, COOA, CONH₂, CONHA, CON(A)₂ or CN,

A is alkyl having from 1 to 6 carbon atoms, and

Hal is F, Cl, Br or I,

and/or physiologically acceptable salts and/or solvates thereof and at least one endothelin receptor antagonist.

2. Pharmaceutical formulation according to Claim 1, comprising at least one compound of the formula I according to Claim 1 in which

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- 5 X is R⁵, phenyl or phenylmethyl, each of which is substituted by COOH, COOA, CONH₂, CONA₂, CONHA or CN; and/or physiologically acceptable salts and/or solvates thereof and at least one endothelin receptor antagonist.
- 10 3. Pharmaceutical formulation according to Claim 1, comprising at least one compound of the formula I according to Claim 1 in which R¹ and R² together are alkylene having 3-5 carbon atoms, -O-CH₂-CH₂-, -O-CH₂-O- or -O-CH₂-CH₂-O-, X is R⁵, phenyl or phenylmethyl, each of which is substituted by COOH, COOA, CONH₂, CONA₂, CONHA or CN; and/or physiologically acceptable salts and/or solvates thereof and at least one endothelin receptor antagonist.
- 15 4. Pharmaceutical formulation according to Claim 1, comprising at least one compound of the formula I according to Claim 1 in which R¹ and R² are each, independently of one another, H, A, OH, OA or Hal,
- 20 R¹ and R² together are alternatively alkylene having 3-5 carbon atoms, -O-CH₂-CH₂-, -O-CH₂-O- or -O-CH₂-CH₂-O-, X is R⁵, phenyl or phenylmethyl, each of which is substituted by COOH, COOA, CONH₂, CONA₂, CONHA or CN; and/or physiologically acceptable salts and/or solvates thereof and at least one endothelin receptor antagonist.
- 25 5. Pharmaceutical formulation according to Claim 1, comprising at least one compound of the formula I according to Claim 1 in which R¹ and R² are each, independently of one another, H, A, OH, OA or Hal,
- 30 R¹ and R² together are alternatively alkylene having 3-5 carbon atoms, -O-CH₂-CH₂-, -O-CH₂-O- or -O-CH₂-CH₂-O-, X is alkylene having 2-5 carbon atoms, cyclohexyl, phenyl or phenylmethyl, each of which is monosubstituted by R⁸,
- 35 R³ is alkyl having 1-6 carbon atoms,
 R⁴ is alkyl having 1-6 carbon atoms,

R⁸ is COOH or COOA,
A is alkyl having from 1 to 6 carbon atoms,
Hal is F, Cl, Br or I;
and/or physiologically acceptable salts and/or solvates thereof and at
5 least one endothelin receptor antagonist.

6. Pharmaceutical formulation according to Claim 1, comprising at least one compound of the formula I according to Claim 1 in which
R¹ and R² are each, independently of one another, H, A, OH, OA or
10 Hal,
R¹ and R² together are alternatively alkylene having 3-5 carbon atoms, -O-CH₂-CH₂-, -O-CH₂-O- or -O-CH₂-CH₂-O-,
R³ is alkyl having 1-6 carbon atoms,
R⁴ is alkyl having 1-6 carbon atoms,
15 X is -(CH₂)₂₋₅-R⁸, in which one CH₂ group may be replaced by O, or is 4-R⁸-cyclohexyl, 4-R⁸-phenyl or 4-(R⁸-methyl)phenyl,
R⁸ is COOH or COOA;
and/or physiologically acceptable salts and/or solvates thereof and at
20 least one endothelin receptor antagonist.
7. Pharmaceutical formulation according to Claim 1, comprising at least one compound of the formula I according to Claim 1 selected from the group consisting of
25 (a) 5-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl]pentanoic acid;
(b) 4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl]benzoic acid;
(c) 4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl]butyric acid;
30 (d) 5-[7-(benzylamino)-1-methyl-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl]pentanoic acid;
(e) [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy]acetic acid;
35 and/or physiologically acceptable salts and/or solvates thereof and at least one endothelin receptor antagonist.

8. Pharmaceutical formulation according to Claim 1, comprising at least [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4,3-d]pyrimidin-5-ylmethoxy]acetic acid and/or physiologically acceptable salts and/or solvates thereof and at least one endothelin receptor antagonist..
- 5
9. Pharmaceutical formulation according to Claims 1 to 8, in which the endothelin receptor antagonist is selected from the group consisting of bosentan, tezosentan and sitaxentan.
- 10
10. Pharmaceutical formulation according to Claims 1 to 8, in which the endothelin receptor antagonist is selected from the group consisting of
- 15
- a) BMS-193884 (EP 558258),
 - b) BMS-207940 (Pharmaprojects (13.06.97)),
 - c) BQ-123 (Exp.Opin.Invest.Drugs, 1997, 6, No.5, 475-487),
 - d) SB-209670 (Exp.Opin.Invest.Drugs, 1997, 6, No.5, 475-487),
 - e) SB-217242 (Exp.Opin.Invest.Drugs, 1997, 6, No.5, 475-487),

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 - f) SB-209598 (Trends in Pharmacol. Sci., 17, 177-81, 1996),
 - g) TAK-044 (Exp.Opin.Invest.Drugs, 1997, 6, No.5, 475-487),
 - h) Bosentan (Trends in Pharmacol. Sci., 18, 408-12, 1997),
 - i) PD-156707 (J.Med.Chem., 40, No.7, 1063-74, 1997),
 - j) L-749329 (Bioorg.Med.Chem.Lett., 7, No.3, 275-280, 1997),

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 - k) L-754142 (Exp.Opin.Invest.Drugs, 1997, 6, No.5, 475-487),
 - l) ABT-627 (J.Med.Chem., 40, No.20, 3217-27, 1997),
 - m) A-127772 (J.Med.Chem., 39, No.5, 1039-1048, 1996),
 - n) A-206377 (213th American Chemical Society National Meeting, San Francisco, California, USA, 13 – 17 April 1997, Poster, MEDI 193),

30

 - o) A-182086 (J.Med.Chem., 40, No.20, 3217-27, 1997),
 - p) EMD-93246 (211th American Chemical Society National Meeting, New Orleans, USA, 1996, Poster, MEDI 143),
 - q) EMD-122801 (Bioorg.Med.Chem.Lett., 8, No.1, 17-22, 1998),

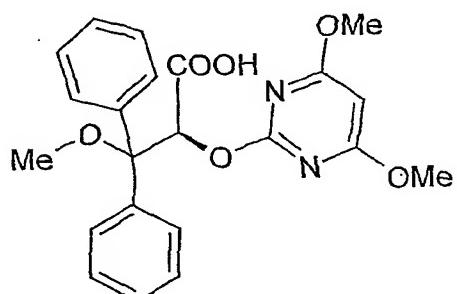
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 - r) ZD-1611 (Trends in Pharmacol. Sci., 18, 408-12, 1997),
 - s) AC-610612 (R&D Focus Drug News (18.05.98)),

- 109 -

- t) T-0201 (70th Annual Meeting of the Japanese Pharmacological Society, Chiba, Japan, 22-15 March 1997, Lecture, O-133),
u) J-104132 (R&D Focus Drug News (15.12.97)),

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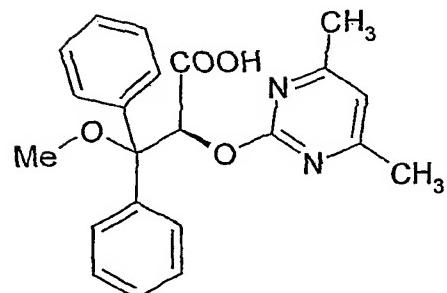


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v)

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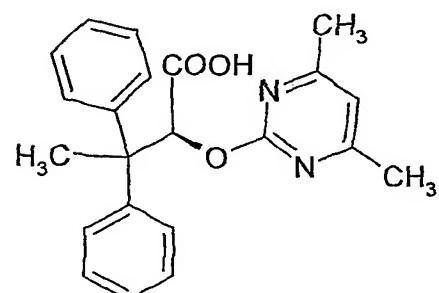
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w)

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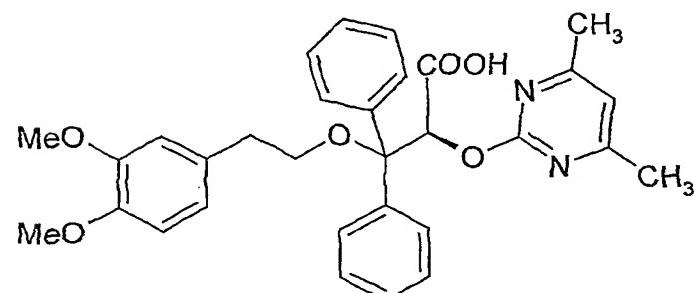
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x)

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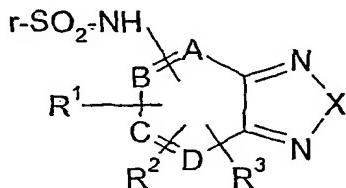
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y)

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11. Pharmaceutical formulation according to Claims 1 to 8, in which the endothelin receptor antagonist is selected from
- 5 a) the compounds of the formula I described in EP 0733626

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in which

15

-A=B-C=D- is a -CH=CH-CH=CH- group in which 1 or 2 CH has (have) been replaced by N,

20

Ar is Ph or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by H, Hal, A, alkenyl having up to 6 carbon atoms, Ph, OPh, NO₂, NR⁴R⁵, NHCOR⁴, CF₃, OCF₃, CN, OR⁴, COOR⁴, (CH₂)_nCOOR⁴, (CH₂)_nNR⁴R⁵, -N=C=O or NHCONR⁴R⁵,

25

R¹, R²
and R³ are each, independently of one another, absent, H, Hal, A, CF₃, NO₂, NR⁴R⁵, CN, COOR⁴, NHCOR⁴,

30

R⁴ and R⁵ are each, independently of one another, H or A, or together are alternatively -CH₂-(CH₂)_n-CH₂-,

A is alkyl having from 1 to 6 carbon atoms,

Ph is phenyl,

X is O or S,

Hal is F, Cl, Br or I,

n is 1, 2 or 3,

and their salts, with the exception of

4-methyl-N-(2,1,3-benzothiadiazol-4-yl)benzenesulfonamide,

4-methyl-N-(2,1,3-benzothiadiazol-5-yl)benzenesulfonamide, 4-nitro-N-(2,1,3-benzothiadiazol-4-yl)benzenesulfonamide, 4-nitro-N-(2,1,3-benzothiadiazol-5-yl)benzenesulfonamide, 4-amino-N-(2,1,3-benzo-

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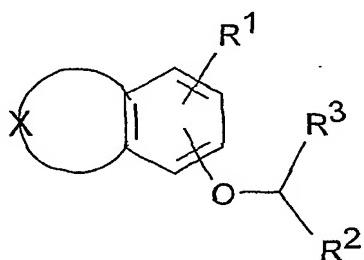
- 111 -

thiadiazol-4-yl)benzenesulfonamide and 4-amino-N-(2,1,3-benzothiadiazol-5-yl)benzenesulfonamide;

b) the compounds of the formula I described in EP 0733626

5

10



in which

15

X is a saturated, partially unsaturated or completely unsaturated 3- to 4-membered alkylene chain, in which from 1 to 3 carbon atoms may be replaced by N and/or from 1 to 2 carbon atoms may be replaced by 1-2 O atoms and/or 1-2 S atoms, but where at most up to 3 carbon atoms may be replaced and where, in addition, a single, double or triple substitution of the alkylene chain and/or of a nitrogen located therein by A, R⁸ and/or NR⁴R^{4'} may occur, and where furthermore one CH₂ group in the alkylene chain may also be replaced by a C=O group,

20

A is alkyl having 1-6 carbon atoms, in which one or two CH₂ groups may be replaced by O or S atoms or by -CR⁴=CR^{4'}- groups and in addition 1-7 H atoms may be replaced by F,

25

R¹ is H or A,
R² is COOR⁴, CN, 1H-tetrazol-5-yl or CONHSO₂R⁸,
R³ is Ar,

30

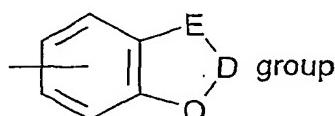
R⁴ and R^{4'} are each, independently of one another, H, alkyl having from 1 to 6 carbon atoms or benzyl,

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Ar is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R⁵, R⁶ or R⁷, or is a

5



10

which is unsubstituted or monosubstituted or disubstituted in the phenyl part by R⁵ or R⁶,

R⁵, R⁶

and R⁷

are each, independently of one another, R⁴, OR⁴, Hal, CF₃, OCF₃, OCHF₂, OCH₂F, NO₂, NR⁴R⁴, NHCOR⁴, CN, NHSO₂R⁴, COOR⁴, COR⁴, CONHSO₂R⁸, O(CH₂)_nR², OPh, O(CH₂)_nOR⁴ or S(O)_mR⁴,

15

R⁸

is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR¹, NR⁴R⁴ or Hal,

E is CH₂ or O,

20

D is carbonyl or [C(R⁴R⁴)]_n,

Hal is F, Cl, Br or I,

m is 0, 1 or 2,

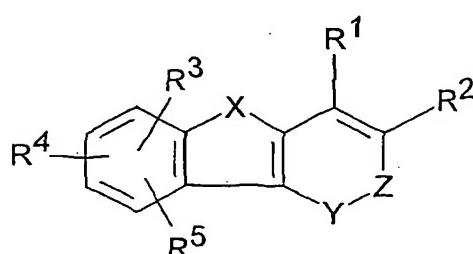
n is 1 or 2,

and their salts;

25

c) the compounds of the formula I described in EP 0755934

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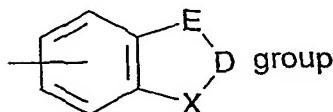
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in which

-Y-Z- is -NR⁷-CO-, -N=C(OR⁷)- or -N=CR⁸-,

	R^1	is Ar,
	R^2	is COOR ⁶ , CN, 1H-tetrazol-5-yl or CONHSO ₂ Ar,
	R^3 , R^4	
	and R^5	are each, independently of one another, R^6 , OR ⁶ ,
5		S(O) _m R ⁶ , Hal, NO ₂ , NR ⁶ R ^{6'} , NHCOR ⁶ , NHSO ₂ R ⁶ ,
		OCOR ⁶ , COOR ⁶ or CN,
	R^6 and $R^{6'}$	are each, independently of one another, H, alkyl having from 1 to 6 carbon atoms, benzyl or phenyl,
10	R^7	is (CH ₂) _n Ar,
	R^8	is Ar or OAr,
	Ar	is phenyl which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R ⁹ , R ¹⁰ or R ¹¹ , or is unsubstituted naphthyl or a

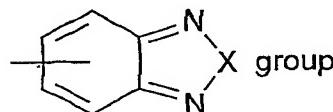
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which is unsubstituted or monosubstituted or disubstituted in the phenyl part by R⁹ or R¹⁰, or is a

25



which is unsubstituted or monosubstituted or disubstituted in the cyclohexadienyl part by R⁹ or R¹⁰,

30

R^9 , R^{10}
and R^{11}

are each, independently of one another, R^6 , OR⁶, Hal, CF₃, OCF₃, OCHF₂, OCH₂F, NO₂, NR⁶R^{6'}, NHCOR⁶, CN, NHSO₂R⁶, COOR⁶, COR⁶, CONHSO₂Ar, O(CH₂)_nR², O(CH₂)_nOR⁶ or S(O)_mR⁶,

35

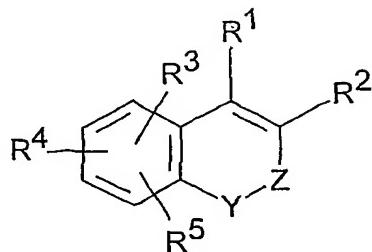
E is CH₂, S or O,
D is carbonyl or [C(R⁶R^{6'})]_n,
Hal is F, Cl, Br or I,

X is O or S,
 m is 0, 1 or 2,
 n is 1 or 2,
 and their salts;

5

d) the compounds of the formula I described in EP 0757039

10



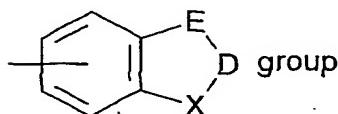
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in which
 -Y-Z- is $-NR^7-CO-$, $-N=C(OR^7)-$ or $-N=CR^8-$,
 R¹ is Ar,
 R² is COOR⁶, $(CH_2)_nCOOR^6$, CN, 1H-tetrazol-5-yl or CONHSO₂Ar,
 R³, R⁴
 and R⁵ are each, independently of one another, R⁶, OR⁶,
 S(O)_mR⁶, Hal, NO₂, NR⁶R⁶, NHCOR⁶, NHSO₂R⁶,
 OCOR⁶, COR⁶, COOR⁶ or CN, where R³ and R⁴
 together may alternatively be an O(CH₂)_nO group,
 R⁶ and R⁶ are each, independently of one another, H, alkyl having
 from 1 to 6 carbon atoms, benzyl or phenyl,
 R⁷ is (CH₂)_nAr,
 R⁸ is Ar or OAr,
 Ar is phenyl which is unsubstituted or monosubstituted,
 disubstituted or trisubstituted by R⁹, R¹⁰ or R¹¹, or is
 unsubstituted naphthyl or a

25

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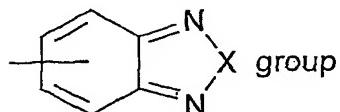
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- 115 -

which is unsubstituted or monosubstituted or disubstituted in the phenyl part by R⁹ or R¹⁰, or is a

5



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which is unsubstituted or monosubstituted or disubstituted in the cyclohexadienyl part by R⁹ or R¹⁰,

R⁹, R¹⁰

and R¹¹

are each, independently of one another, R⁶, OR⁶, Hal, CF₃, OCF₃, OCHF₂, OCH₂F, NO₂, NR⁶R⁶, NHCOR⁶, CN, NHSO₂R⁶, COOR⁶, COR⁶, CONHSO₂Ar, O(CH₂)_nR²,

15

O(CH₂)_nOR⁶ or S(O)_mR⁶,

E is CH₂, S or O,

D is carbonyl or [C(R⁶R⁶)]_n,

X is O or S,

Hal is F, Cl, Br or I,

20

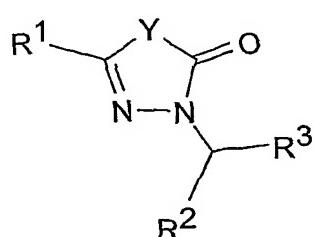
m is 0, 1 or 2,

n is 1 or 2,

and their salts;

e) the compounds of the formula I described in EP 0796250

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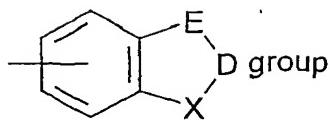
in which

Y is -C(R⁴R⁴)-C(R⁴R⁴)-, -CR⁴=CR⁴- or -C(R⁴R⁴)-S-,

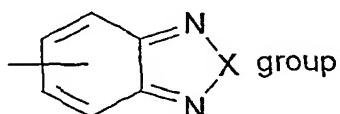
R¹ is Het, Ar, R³ or R⁴,

R² is Ar or a

35



5 which is unsubstituted or monosubstituted or disubstituted in the phenyl part by A, R³, OR⁴, NH₂, NHA, NA₂, NO₂, CN, Hal, NHCOR⁴, NHSO₂R⁴, COOR⁴, COR⁴, CONHSO₂R⁶, O(CH₂)_nR³, OPh, O(CH₂)_nOR⁴ or S(O)_mR⁴, or a



15 which is unsubstituted or monosubstituted or disubstituted in the cyclohexadienyl part by A, R³, OR⁴, NH₂, NHA, NA₂, NO₂, CN, Hal, NHCOR⁴, NSO₂R⁴, COOR⁴, COR⁴, CONHSO₂R⁶, O(CH₂)_nR³, OPh, O(CH₂)_nOR⁴ or S(O)_mR⁴,

20 R³ is CN, COOH, COOA, CONHSO₂R⁵ or 1H-tetrazol-5-yl,
 R⁴ and R^{4'} are each, independently of one another, H, A, or phenyl
 or benzyl; each of which is unsubstituted or monosubsti-
 tuted by alkoxy.

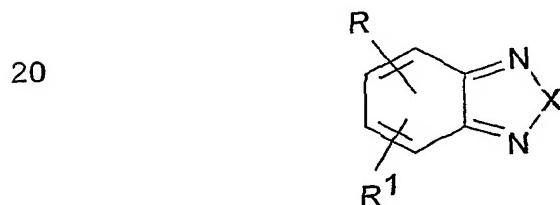
25	R^5	is A or Ar,
	R^6	is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR ⁵ , NH-, NHA-, NA-, NO ₂ , CN or Hal.

30 A is alkyl having 1-6 carbon atoms, in which one or two CH_2 groups may be replaced by O or S atoms or by $-\text{CR}^4=\bar{\text{C}}\text{R}^4-$ groups and in addition 1-7 H atoms may be replaced by F,

- 117 -

- NHSO₂R⁴, COOR⁴, COR⁴, CONHSO₂R⁸, O(CH₂)_nR³,
OPh, O(CH₂)_nOR⁴ or S(O)_mR⁴,
- 5 Het is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/or S atoms, bonded via N or C, which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, R³, NH₂, NHA, NA₂, CN, NO₂ and/or carbonyl oxygen,
- 10 D is carbonyl or [C(R⁴R⁴)]_n,
- E is CH₂, S or O,
- Hal is F, Cl, Br or I,
- X is O or S,
- m is 0, 1 or 2,
- n is 1 or 2,
- 15 and their salts;

f) the compounds of the formula I described in WO 9719077



in which

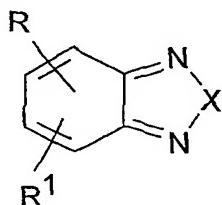
- 25 R is $R^2-O-C(=O)-N(\text{CH}_2)_nR^4$ or $R^2-O-C(=O)-N(\text{CH}_2)_nR^8$
- 30 R² is H or A,
- X is O or S,
- R¹ is H, Hal, OH, OA, A, alkylene-O-A, NO₂, NH₂, NH-acyl, SO₂NH₂, SO₃-A, SO₂NHA, CN or formyl,
- 35 R² is H or A,

- 118 -

- 5 R^3, R^5, R^6 are each, independently of one another, H, Hal, OH,
 OA, O-alkylene- R^4 , A, S-A, NO_2 , NH_2 , NHA, NA_2 ,
 NH -acyl, $NHSO_2A$, $NHSO_2R^4$, $NASO_2A$, $NASO_2-R^4$,
 $NH(CO)NH_2$, $NH(CO)NHA$, formyl, $NH(CO)NH$ -phenyl,
 $NHCOOA$, NA -acyl, NHR^4 , $NHCOOR^4$, $NHCOO$ -benzyl,
 $NHSO_2$ -benzyl, $NHCOO$ -alkylene-OA, $NH(CO)NA_2$,
 N-piperidinyl-CO-NH, N-pyrrolidinyl-CONH,
 $O(CH_2)_nCOOR^2$, $O(CH_2)_nOR^2$, CH_2OH or CH_2OA ,
- 10 R^3 and R^6 together are alternatively -O- CH_2 -O-, -O- CH_2 - CH_2 -O-,
 -O- CH_2 - CH_2 -, -O-CF₂-O- or -O-CF₂-CF₂-O-,
- 15 R^4 is phenyl which is unsubstituted or monosubstituted or
 polysubstituted by R^3 and/or R^6 ,
 A is alkyl having 1-6 carbon atoms,
 Hal is fluorine, chlorine, bromine or iodine,
 n is 1 or 2,
 and their salts;

g) the compounds of the formula I described in WO 9730982

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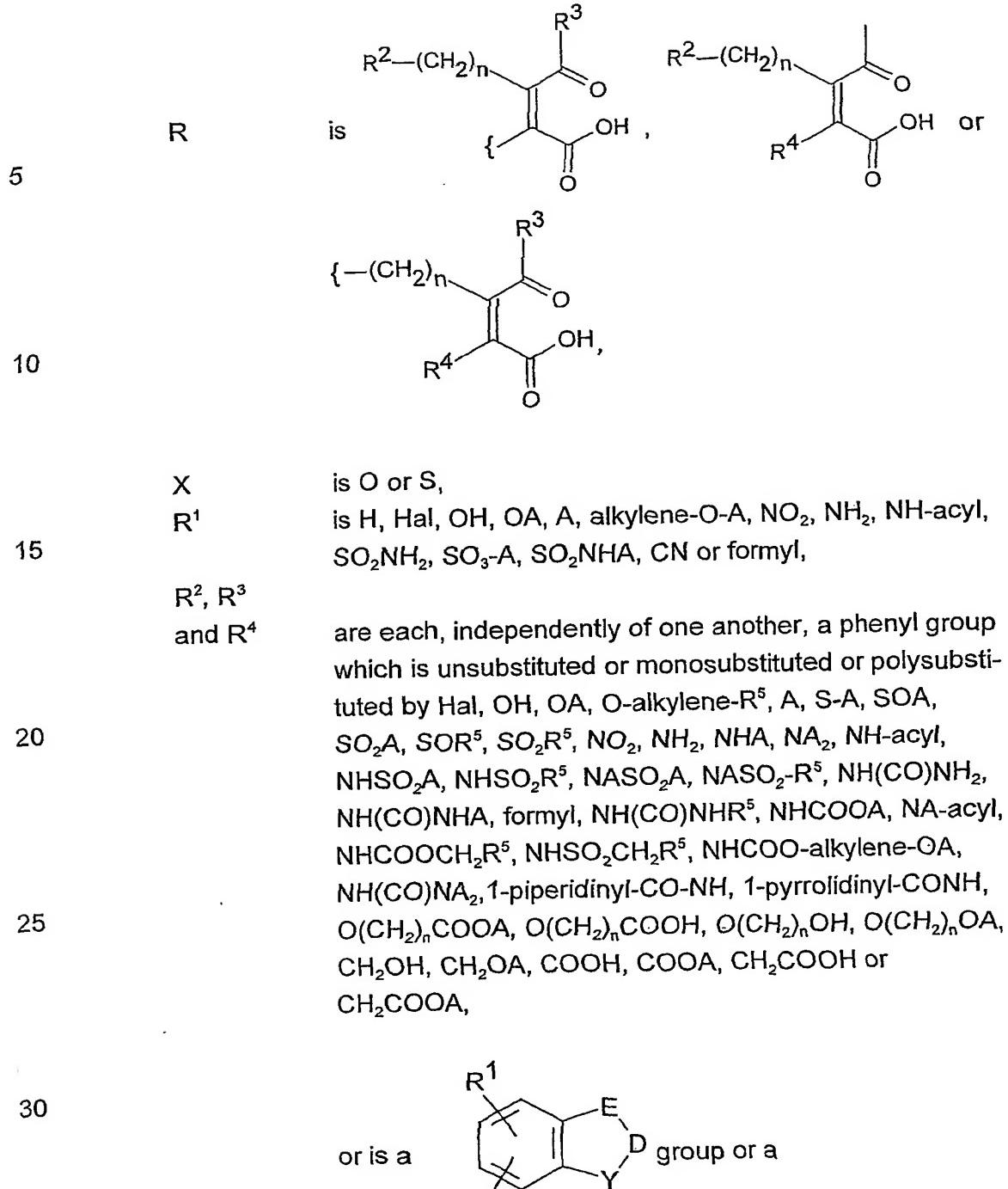
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in which

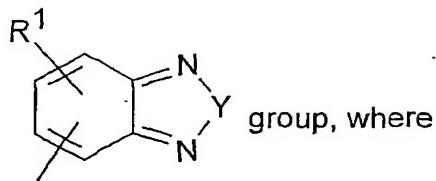
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- 119 -



- 120 -



group, where

5

R^2 is additionally A or cycloalkyl,
 R^5 is a phenyl group which is unsubstituted or monosubstituted or polysubstituted by Hal, OH, OA, A, S-A, NO₂, NH₂, NHA, NA₂, NH-acyl, NSO₂A, NASO₂A, NH(CO)NH₂, NH(CO)NHA, formyl, NHCOOA, NA-acyl, NHCOO-alkylene-OA, NH(CO)NA₂, N-piperidinyl-CO-NH, N-pyrrolidinyl-CONH, O(CH₂)_nCOOA, O(CH₂)_nCOOH, O(CH₂)_nOH, O(CH₂)_nOA, CH₂OH, CH₂OA, COOH, COOA, CH₂COOH or CH₂COOA,

10

A is alkyl having 1-6 carbon atoms, in which one or two CH₂ groups may be replaced by O or S atoms or by -CR⁶=CR^{6'}- groups and/or 1-7 H atoms may be replaced by F,

15

D is carbonyl or [C(R⁶R^{6'})]_m,

20

E is CH₂, S or O,

Y is O or S,

R⁶ and R^{6'} are each, independently of one another, H, F or A,

Hal is fluorine, chlorine, bromine or iodine,

n is 1 or 2, and

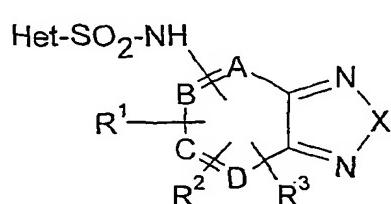
m is 1 or 2,

25

or a tautomeric cyclised form, and the (E)-isomers and the salts of all isomers;

h) the compounds of the formula I described in WO 9730996

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35

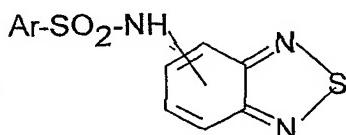
in which

- 121 -

- A=B-C=D- is a -CH=CH-CH=CH- group, in which, in addition, 1 or
 2 CH may be replaced by N,
 Het is a monocyclic or bicyclic, saturated, unsaturated or
 aromatic heterocyclic radical having from 1 to 4 N, O
 and/or S atoms which is unsubstituted or substituted by
 -Z-R⁶,
 R¹, R²
 and R³ are each, independently of one another, absent, H, Hal,
 A, CF₃, NO₂, NR⁴R⁵, CN, COOR⁴ or NHCOR⁴,
 R⁴ and R⁵ are each, independently of one another, H or A, or
 together are alternatively -CH₂-(CH₂)_n-CH₂-,
 R⁶ is a phenyl radical, benzothiadiazol-5-yl or benzoxa-
 diazol-5-yl radical, each of which is unsubstituted or
 monosubstituted, disubstituted or trisubstituted by R⁷, R⁸
 and/or R⁹,
 R⁷, R⁸
 and R⁹ are each, independently of one another, A, O-A, CN,
 COOH, COOA, Hal, formyl, -CO-A, and R⁷ and R⁸ are
 alternatively -O-(CH₂)_m-O-,
 A is alkyl having from 1 to 6 carbon atoms,
 X is O or S,
 Z is -CO-, -CONH-, -CO-(CH₂)_n-, -CH=CH-, -(CH₂)_n-,
 -CONHCO-, -NHCONH-, -NHCOO-, -O-CONH-, -CO-O-
 or -O-CO-,
 Hal is F, Cl, Br or I,
 m is 1 or 2, and
 n is 1, 2 or 3,
 and their salts;
 i) the compounds of the formula I described in DE 19609597

35

in which



- 122 -

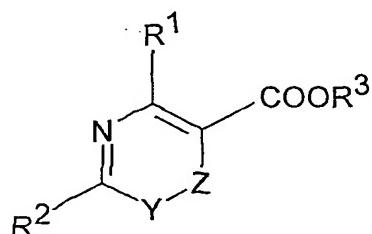
Ar is naphthyl which is monosubstituted by NH₂, NHA or NA₂, and

A is alkyl having from 1 to 6 carbon atoms,
and their physiologically acceptable salts;

5

j) the compounds of the formula I described in DE 19612101

10



15

in which

-Y-Z- is -NR⁴-CO or -N=CR⁵-,

R¹ is Ar,

R² is H, alkyl having 1-6 carbon atoms which is unsubstituted or monosubstituted, disubstituted or trisubstituted by OR³ or Hal, or (CH₂)_mPh or (CH₂)_m-cycloalkyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R³, OR³ or Hal,

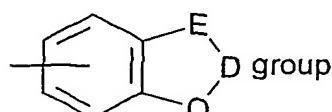
R³ and R^{3'} are each, independently of one another, H, alkyl having 1-6 carbon atoms or benzyl,

R⁴ is CH₂Ar,

R⁵ is OCH₂Ar,

Ar is phenyl which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R⁶, R⁷ or R⁸, or a

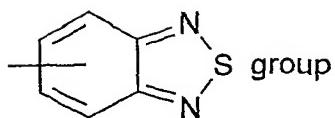
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30 which is unsubstituted or monosubstituted in the phenyl part by R⁶, or a

35

- 123 -



- | | |
|----|---|
| 5 | which is unsubstituted or monosubstituted in the cyclohexadienyl part by R ⁶ , |
| | E is CH ₂ or O, |
| | D is carbonyl or (CH ₂) _n , |
| | E and D together are alternatively CH=CR ⁹ , |
| 10 | R ⁶ , R ^{6'} are each, independently of one another, R ³ , OR ³ or Hal, |
| | R ⁷ is R ³ , OR ³ , Hal, NO ₂ , NH ₂ , NHR ³ , NR ³ R ^{3'} , NHCOR ³ , COOR ³ , O(CH ₂) _n R ³ or O(CH ₂) _n OR ³ , |
| | R ⁸ is Ph which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R ³ , OR ³ , Hal, NO ₂ , NH ₂ , NHR ⁶ , NR ⁶ R ^{6'} , NHCOR ³ or COOR ³ , |
| 15 | R ⁹ is H, OH, CH ₂ OH or COOR ³ , |
| | Hal is F, Cl, Br or I, |
| | Ph is phenyl, |
| | m is 0 or 1, |
| 20 | n is 1 or 2, |
| | and their salts; |

k) the compounds of the formula I described in WO 9827091

- 25

30

in which

R

is phenyl which is unsubstituted or monosubstituted,
disubstituted or trisubstituted by R³, R⁴ or R⁵, or 2,1,3-
benzothiadiazolyl which is unsubstituted or mono-
substituted by R²,

35

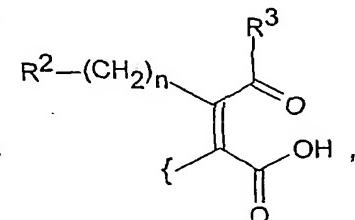
R¹ is A, in which 1-7 H atoms may be replaced by F, is
 -S-A, -O-A, is phenyl or -alkylene-phenyl, each of which
 is unsubstituted or monosubstituted by R³, or is thienyl
 which is unsubstituted or monosubstituted by R³,
 5 R² is A, F, Cl, Br or -O-A,
 R³, R⁴
 and R⁵ are each, independently of one another, A, -O-A, -S-A,
 -O-alkylene-COOH, -alkylene-COOH or COOH,
 10 R³ and R⁴ together are alternatively -O-CH₂-O-, and
 A is alkyl having 1-7 carbon atoms,
 and their salts;

I) the compounds of the formula I described in WO 9827077

15

20 in which

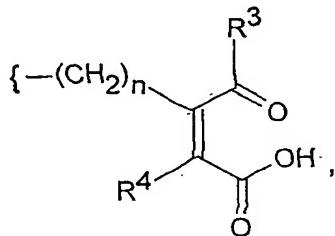
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$$\begin{array}{c} \text{R}^2 - (\text{CH}_2)_n - \text{C}(=\text{O}) - \text{C}_6\text{H}_3(\text{OH})(\text{R}^4) \\ | \\ \text{C}_6\text{H}_3(\text{OH})(\text{R}^4) \end{array}$$

or

30



35

X is O or S,

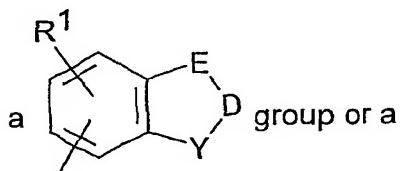
R^1 is H, Hal, OH, OA, A, alkylene-O-A, NO_2 , NH_2 , NH-acyl, SO_2NH_2 , $\text{SO}_2\text{-A}$, SO_2NHA , CN or formyl.

R², R³

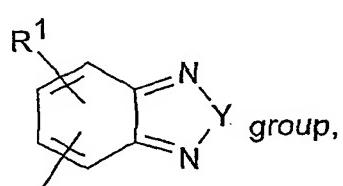
- 125 -

and R⁴ are each, independently of one another, a phenyl group which is unsubstituted or monosubstituted or polysubstituted by R⁷, where R² is additionally A or cycloalkyl, or are

5



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with the proviso that at least one of the radicals R², R³ or R⁴ is an R⁸ radical which is unsubstituted or mono-substituted or polysubstituted by R⁷,

R⁵

20

is a phenyl group which is unsubstituted or monosubstituted or polysubstituted by Hal, OH, OA, A, S-A, NO₂, NH₂, NHA, NA₂, NH-acyl, NHSO₂A, NASO₂A, NH(CO)NH₂, NH(CO)NHA, formyl, NHCOOA, NA-acyl, NHCOO-alkylene-OA, NH(CO)NA₂, N-piperidinyl-CO-NH, N-pyrrolidinyl-CONH, O(CH₂)_nCOOA, O(CH₂)_nCOOH, O(CH₂)_nOH, O(CH₂)_nOA, CH₂OH, CH₂OA, COOH, COOA, CH₂COOH or CH₂COOA,

25

A

is alkyl having 1-6 carbon atoms, in which one or two CH₂ groups may be replaced by O or S atoms or by -CR⁶=CR⁶- groups and/or 1-7 H atoms may be replaced by F,

30

D

is carbonyl or [C(R⁶R⁶)]_m,

E

is CH₂, S or O,

Y

is O or S,

R⁶ and R⁸

are each, independently of one another, H, F or A,

35

R⁷

is Hal, OH, OA, O-alkylene-R⁶, A, S-A, S-OA, SO₂A, S-OR⁵, SO₂R⁵, NO₂, NH₂, NHA, NA₂, NH-acyl, NHSO₂A,

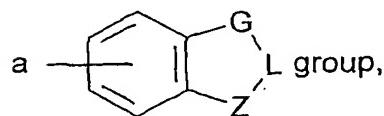
- 126 -

NHSO₂R⁵, NASO₂A, NASO₂-R⁵, NH(CO)NH₂,
 NH(CO)NHA, formyl, NH(CO)NHR⁵, NHCOOA, NA-acyl,
 NHCOOCH₂R⁵, NHSO₂CH₂R⁵, NHCOO-alkylene-OA,
 NH(CO)NA₂, 1-piperidinyl-CO-NH, 1-pyrrolidinyl-CONH,
 O(CH₂)_nCOOA, O(CH₂)_nCOOH, O(CH₂)_nOH, O(CH₂)_nOA,
 CH₂OH, CH₂OA, COOH, COOA, CH₂COOH or
 CH₂COOA,

5

R⁸ is a 5-7-membered heterocyclic radical having 1-4 N, O and/or S atoms or is

10



15

G and Z are each, independently of one another, -CH=, N, O or S,

L is -CH=, -CH=CH- or -CH₂-CH₂-CH₂-

Hal is fluorine, chlorine, bromine or iodine,

n is 0, 1 or 2, and

20

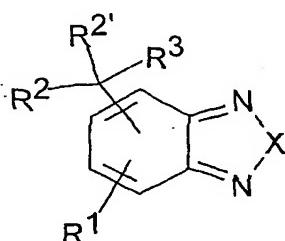
m is 1 or 2,

or a tautomeric cyclised form, and the (E)-isomers and the salts of all isomers;

25

m) the compounds of the formula I described in WO 9841515

30



in which

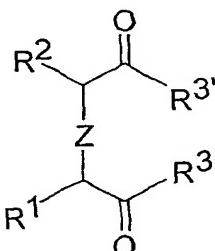
X is O or S,

35

	R^1	is H, Hal, OH, OA, A, NO_2 , NH_2 , NHA, NAA', NHCOR^4 , NHCOR^6 , NSO_2R^4 , NSO_2R^6 , $\text{S(O)}_m\text{R}^6$, SO_3H , $\text{SO}_2\text{NR}^4\text{R}^4$ or formyl,
5	R^2 and R^2'	are each, independently of one another, A, $(\text{CH}_2)_n\text{Ar}$, $(\text{CH}_2)_n\text{Het}$, CH_2COAr , CH_2COHet or OAr,
	R^2'	is additionally also H,
	R^3	is COOR^4 , CN, 1H-tetrazol-5-yl or $\text{CONHSO}_2\text{R}^5$,
10	R^4 and R^4'	are each, independently of one another, H or A,
	R^5	is A or Ar,
15	R^6	is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, NH_2 , NHA, NAA', NO_2 , CN or Hal;
	R^7 and R^7'	are each, independently of one another, H or alkyl having 1-6 carbon atoms,
20	A and A'	are each, independently of one another, alkyl having 1-6 carbon atoms, in which one or two CH_2 groups may be replaced by O or S atoms or by $-\text{CR}^7=\text{CR}^7-$ groups and/or 1-7 H atoms may be replaced by F, or benzyl,
25	Ar	is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR^4 , NH_2 , NHA, NAA', NO_2 , CN, Hal, NHCOR^4 , NHCOR^6 , NSO_2R^4 , NSO_2R^6 , COOR^4 , OPh, CONH ₂ , CONHA, CONAA', COR ⁴ , $\text{CONHSO}_2\text{R}^4$, $\text{CONHSO}_2\text{R}^6$, $\text{O}(\text{CH}_2)_n\text{COOR}^4$, $\text{O}(\text{CH}_2)_n\text{OR}^4$, SO_3H , $\text{SO}_2\text{NR}^4\text{R}^4$, $\text{S(O)}_m\text{R}^6$ or $\text{S(O)}_m\text{R}^4$,
	Het	is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having 1-4 N, O and/or S atoms, bonded via N or C, which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, R^3 , NH_2 , NHA, NAA', NO_2 and/or =O,
30	Hal	is fluorine, chlorine, bromine or iodine,
	m	is 0, 1 or 2, and
	n	is 1 or 2,
35		where, if R^2 is CH_2COAr and R^2' is H, R^3 is not COOA, and salts thereof;

n) the compounds of the formula I described in WO 9841521

5

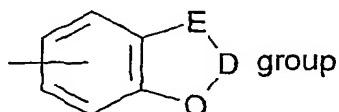


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in which

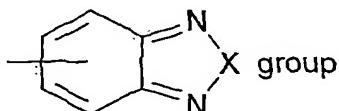
Z is a single or double bond,
R¹ is a

15



20

which is unsubstituted or monosubstituted in the phenyl part by R⁷, or is a



25

which is unsubstituted or monosubstituted in the cyclohexadienyl part by R⁷,

R² is A, Ar-(CH₂)_m, cycloalkyl-(CH₂)_m, Het-(CH₂)_m or R¹-(CH₂)_m,

R³ and R^{3'} are each, independently of one another, OR⁴, NSO₂R⁵, NH₂, NHA or NAA',

30

R³ and R^{3'} together are alternatively -O-, forming a cyclic anhydride,

R⁴ and R^{4'} are each, independently of one another, H or A,

R⁵ is A or Ar,

R⁶ is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, NH₂,

35

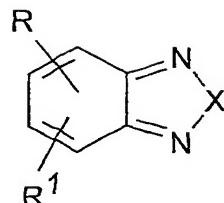
NHA, NAA', NO₂, CN or Hal,

- 129 -

R⁷ is A, COOR⁴, CN, 1H-tetrazol-5-yl, CONHSO₂R⁵, Hal, OR⁴, NO₂, NH₂, NHA, NAA', NHCOR⁴, NHCOR⁶, NHSO₂R⁴, NHSO₂R⁶, S(O)_kR⁴, S(O)_kR⁶, SO₂NR⁴R⁴ or formyl,
 R⁸ and R^{8'} are each, independently of one another, H or alkyl having
 5 1-6 carbon atoms,
 E is CH₂ or O,
 D is carbonyl or (CR⁴R^{4'})_n,
 E and D together are alternatively CR⁴=R^{4'},
 X is S or O,
 10 A and A' are each, independently of one another, alkyl having 1-6 carbon atoms, in which one or two CH₂ groups may be replaced by O or S atoms or by -CR⁸=CR^{8'}- groups and/or 1-7 H atoms may be replaced by F, or benzyl,
 15 Ar is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR⁴, NH₂, NHA, NAA', NO₂, CN, Hal, NHCOR⁴, NHCOR⁶, NHSO₂R⁴, NHSO₂R⁶, COOR⁴, OPh, CONH₂, CONHA, CONAA', COR⁴, CONHSO₂R⁴, CONHSO₂R⁶, O(CH₂)_nCOOR⁴, O(CH₂)_nOR⁴, SO₂NR⁴R⁴, S(O)_kR⁶ or S(O)_kR⁴,
 20 Het is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having 1-4 N, O and/or S atoms, bonded via N or C, which may be unsubstituted, monosubstituted or disubstituted or trisubstituted by Hal, A, COOR⁴, CN, 1H-tetrazol-5-yl, CONHSO₂R⁵, NH₂, NHA, NAA', NO₂ and/or =O,
 25 Hal is fluorine, chlorine, bromine or iodine,
 k is 0, 1 or 2,
 m is 0, 1 or 2, and
 n is 1 or 2,
 30 and the (Z)- and (E)-isomers and the salts of all isomers;

o) the compounds of the formula I described in WO 9842702

- 130 -

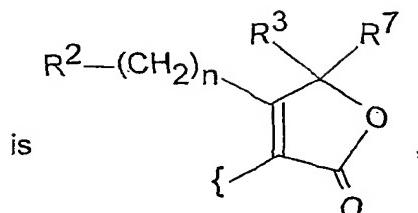


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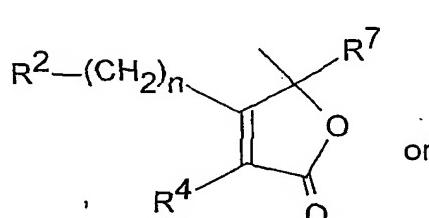
in which

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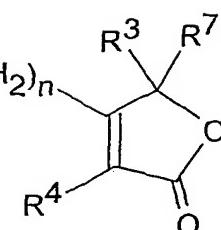
R



15



or



20

X and Y are each, independently of one another, O or S,

R¹ is H, Hal, OH, OA, A, alkylene-O-A, NO₂, NH₂, NH-acyl, SO₂NH₂, SO₂-A, SO₂NHA, CN or formyl,

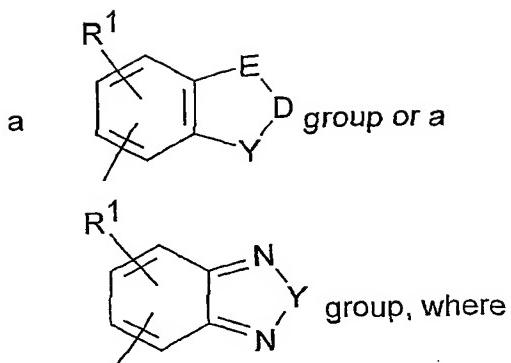
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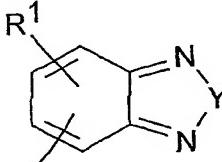
R², R³ and R⁴ are each, independently of one another, a phenyl group which is unsubstituted or monosubstituted or polysubstituted by Hal, OH, OA, O-alkylene-R⁵, A, S-A, S-OA, SO₂A, S-OR⁵, SO₂R⁵, NO₂, NH₂, NHA, NA₂, NH-acyl, NHSO₂A, NHSO₂R⁵, NASO₂A, NASO₂-R⁵, NH(CO)NH₂, NH(CO)NHA, formyl, NH(CO)NHR⁵, NHCOOA, NA-acyl, NHCOOCH₂R⁵, NHSO₂CH₂R⁵, NHCOO-alkylene-OA,

30

NH(CO)NA₂, 1-piperidinyl-CO-NH, 1-pyrrolidinyl-CONH, O(CH₂)_nCOOA, O(CH₂)_nCOOH, O(CH₂)_nOH, O(CH₂)_nOA, CH₂OH, CH₂OA, COOH, COOA, CH₂COOH or CH₂COOA,

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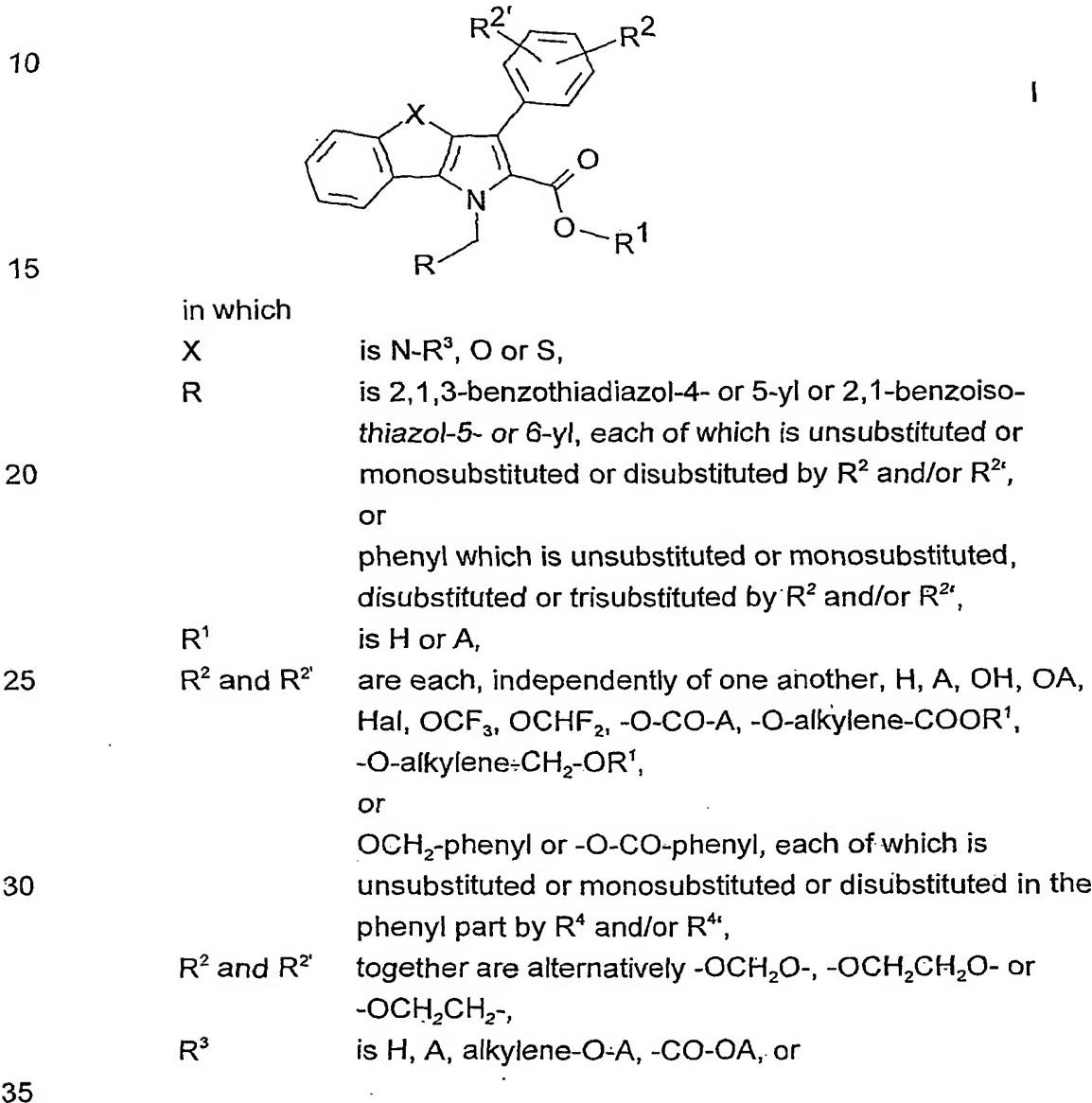


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|----|---|--|
| 5 | 
group, where | |
| 10 | R^5 | R^2 is additionally A or cycloalkyl,
is a phenyl group which is unsubstituted or monosubstituted or polysubstituted by Hal, OH, OA, A, S-A, NO ₂ , NH ₂ , NHA, NA ₂ , NH-acyl, NSO ₂ A, NASO ₂ A,
NH(CO)NH ₂ , NH(CO)NHA, formyl, NHCOOA, NA-acyl,
NHCOO-alkylene-OA, NH(CO)NA ₂ , |
| 15 | | N-piperidinyl-CO-NH, N-pyrrolidinyl-CONH,
O(CH ₂) _n COOA, O(CH ₂) _n COOH, O(CH ₂) _n OH, O(CH ₂) _n OA,
CH ₂ OH, CH ₂ OA, COOH, COOA, CH ₂ COOH or
CH ₂ COOA, |
| 20 | A | is alkyl having 1-6 carbon atoms, in which one or two
CH ₂ groups may be replaced by O or S atoms or by
-CR ⁶ =CR ⁶ - groups and/or 1-7 H atoms may be replaced
by F, |
| 25 | D | is carbonyl or $[C(R^6R^6')]_m$, |
| | E | is CH ₂ , S or O, |
| | R^6 and R^6' | are each, independently of one another, H, F or A, |
| | R^7 | is -O-C(=Y)-NH-R ⁸ , |
| 30 | R^8 | is alkyl having 1-10 carbon atoms which is unsubstituted
or monosubstituted or disubstituted by R ⁸ and in which
1-2 carbon atoms may be replaced by O and/or S,
and/or may be substituted by =O,
or
cycloalkyl, in which 1-2 carbon atoms may be replaced
by N, O and/or S, |
| 35 | R^9 | is phenyl which is unsubstituted or monosubstituted or
disubstituted by Hal, |

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or is naphthyl, A-O-C(=O)- or Hal,
 Hal is fluorine, chlorine, bromine or iodine,
 n is 0, 1 or 2, and
 m is 1 or 2,
 5 and salts thereof;

p) the compounds of the formula I described in WO 9842709

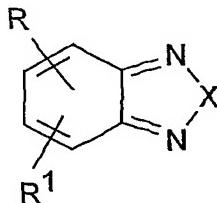


alkylene-phenyl which is unsubstituted or mono-substituted or disubstituted in the phenyl part by R⁴ and/or R^{4'},

- 5 R⁴ and R^{4'} are each, independently of one another, H, A, OH, OA, Hal, COOR¹ or CH₂OR¹,
A is alkyl having 1-6 carbon atoms,
Hal is fluorine, chlorine, bromine or iodine,
and their salts;

10 q) the compounds of the formula I described in WO 9905132

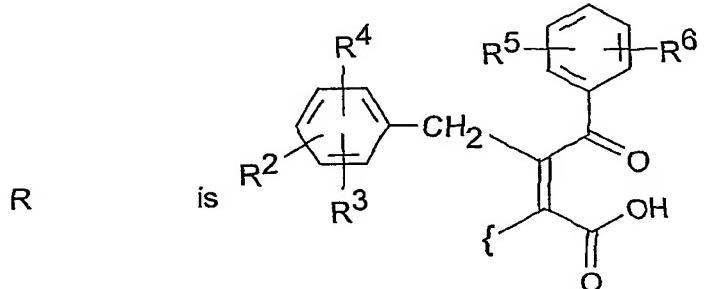
15



I

in which

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- X is O or S,
R¹ is H, Hal, OA or A,
R², R³ R⁵,
and R⁶ are each, independently of one another, H, Hal, A, OA
or R⁴,
R⁴ is -O-(CH₂)_n-Cy,
Cy is cycloalkyl having 3-8 carbon atoms,
A is alkyl having 1-6 carbon atoms, in which one or two
CH₂ groups may be replaced by O or S atoms or by

-CR⁵=CR⁵- groups and/or 1-7 H atoms may be replaced by F,

R⁵ and R^{5'} are each, independently of one another, H, F or A,

Hal is fluorine, chlorine, bromine or iodine,

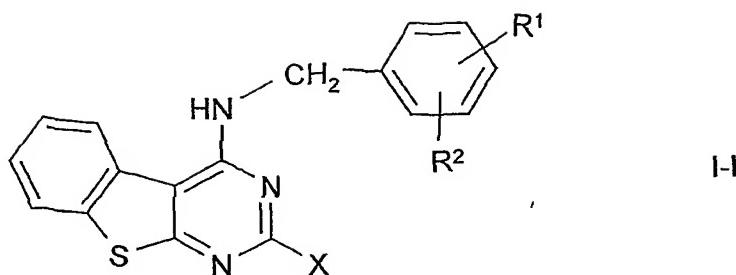
5 n is 0, 1 or 2,

or a tautomeric cyclised form, and the (E)-isomers and the salts of all isomers.

12. Pharmaceutical formulation according to one of the preceding claims, comprising one or more excipients and/or assistants.
13. Use of a pharmaceutical preparation according to one of Claims 1 to 12 for the preparation of a medicament for the treatment of angina, high blood pressure, high pulmonary pressure, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cor pulmonale, dextrocardiac insufficiency, atherosclerosis, conditions of reduced patency of the heart vessels, peripheral vascular diseases, strokes, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, irritable bowel syndrome, tumours, renal insufficiency, liver cirrhosis, erectile dysfunction and for the treatment of female sexual disorders.
14. Use according to Claim 13 for the preparation of a medicament for the treatment of high pulmonary pressure, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cor pulmonale and/or dextrocardiac insufficiency.
15. Set (kit) consisting of separate packs of
 - (a) an effective amount of [7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-ylmethoxy]acetic acid and/or physiologically acceptable salts and/or solvates thereof and
 - (b) an effective amount of an endothelin receptor antagonist.
16. Pharmaceutical formulation comprising at least one compound of the formula I-I

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in which

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R¹ and R² are each, independently of one another, H, A, OA, OH or Hal,

15

R¹ and R² together are alternatively alkylene having 3-5 carbon atoms, -O-CH₂-CH₂-, -CH₂-O-CH₂-, -O-CH₂-O- or -O-CH₂-CH₂-O-,

20

X is R⁴, R⁵ or R⁶, each of which is monosubstituted by R⁷,

R⁴ is linear or branched alkylene having 1-10 carbon atoms, in which one or two CH₂ groups may be replaced by -CH=CH- groups,

R⁵ is cycloalkyl or cycloalkylalkylene having 5-12 carbon atoms,

R⁶ is phenyl or phenylmethyl,

R⁷ is COOH, COOA, CONH₂, CONHA, CON(A)₂ or CN,

A is alkyl having from 1 to 6 carbon atoms, and

Hal is F, Cl, Br or I,

25

and/or physiologically acceptable salts and/or solvates thereof and at least one endothelin receptor antagonist.

30

17. Pharmaceutical formulation according to Claim 16, comprising at least one compound of the formula I-II according to Claim 16 in which X is R⁴, phenyl or phenylmethyl, each of which is substituted by COOH, COOA, CONH₂, CONA₂, CONHA or CN.

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18. Pharmaceutical formulation according to Claim 16, comprising at least one compound of the formula I-II according to Claim 16 in which R¹ and R² together are alkylene having 3-5 carbon atoms, -O-CH₂-CH₂-, -O-CH₂-O- or -O-CH₂-CH₂-O-,

- X is R⁴, phenyl or phenylmethyl, each of which is substituted by COOH, COOA, CONH₂, CONA₂, CONHA or CN.
19. Pharmaceutical formulation according to Claim 16, comprising at least one compound of the formula I-II according to Claim 16 in which R¹ and R² are each, independently of one another, H, A, OA or Hal,
R¹ and R² together are alkylene having 3-5 carbon atoms, -O-CH₂-CH₂-, -O-CH₂-O- or -O-CH₂-CH₂-O-,
X is R⁴, phenyl or phenylmethyl, each of which is substituted by COOH, COOA, CONH₂, CONA₂, CONHA or CN.
20. Pharmaceutical formulation according to Claim 16, comprising at least one compound of the formula I-II according to Claim 16 in which R¹ and R² are each, independently of one another, H, A, OA or Hal,
R¹ and R² together are alternatively alkylene having 3-5 carbon atoms, -O-CH₂-CH₂-, -O-CH₂-O- or -O-CH₂-CH₂-O-,
X is alkylene having 2-5 carbon atoms, cyclohexyl, phenyl or phenylmethyl, each of which is monosubstituted by R⁷,
R⁷ is COOH or COOA,
A is alkyl having from 1 to 6 carbon atoms,
Hal is F, Cl, Br or I.
21. Pharmaceutical formulation according to Claim 16, comprising at least one compound of the formula I-II according to Claim 16 in which R¹ and R² are each, independently of one another, H, A, OA or Hal,
R¹ and R² together are alternatively alkylene having 3-5 carbon atoms, -O-CH₂-CH₂-, -O-CH₂-O- or -O-CH₂-CH₂-O-,
X is alkylene having 2-5 carbon atoms, cyclohexyl, phenyl or phenylmethyl, each of which is monosubstituted by R⁷,
R⁷ is COOH or COOA,
A is alkyl having from 1 to 6 carbon atoms,

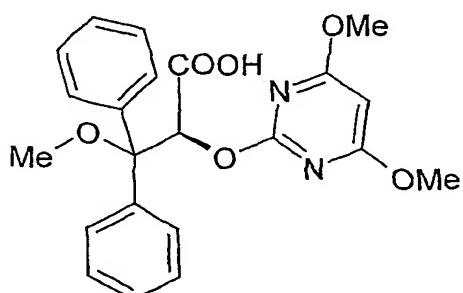
Hal is F, Cl, Br or I.

22. Pharmaceutical formulation according to Claim 16, comprising at least one compound of the formula I-II according to Claim 16, selected from the group consisting of
- (a) 3-[4-(3-chloro-4-methoxybenzylamino)benzo[4,5]thieno[2,3-d]-pyrimidin-2-yl]propionic acid;
- (b) 4-[4-(3,4-methylenedioxybenzylamino)benzo[4,5]thieno[2,3-d]-pyrimidin-2-yl]butyric acid;
- (c) 7-[4-(3,4-methylenedioxybenzylamino)benzo[4,5]thieno[2,3-d]-pyrimidin-2-yl]heptanoic acid;
- (d) 7-[4-(3-chloro-4-methoxybenzylamino)benzo[4,5]thieno[2,3-d]-pyrimidin-2-yl]heptanoic acid;
- (e) 5-[4-(3-chloro-4-methoxybenzylamino)benzo[4,5]thieno[2,3-d]-pyrimidin-2-yl]valeric acid;
- (f) 2-{4-[4-(3-chloro-4-methoxybenzylamino)benzo[4,5]thieno[2,3-d]-pyrimidin-2-yl]cyclohexyl-1-yl}acetic acid;
- (g) 4-[4-(3,4-methylenedioxybenzylamino)benzo[4,5]thieno[2,3-d]-pyrimidin-2-yl]cyclohexanecarboxylic acid;
- (h) 4-[4-(3,4-methylenedioxybenzylamino)benzo[4,5]thieno[2,3-d]-pyrimidin-2-yl]benzoic acid;
- (i) 4-[4-(3,4-methylenedioxybenzylamino)benzo[4,5]thieno[2,3-d]-pyrimidin-2-yl]phenylacetic acid;
- (j) 4-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]-pyrimidin-2-yl]cyclohexanecarboxylic acid.
23. Pharmaceutical formulation according to Claim 16, comprising at least 4-[4-(3-chloro-4-methoxybenzylamino)benzothieno[2,3-d]-pyrimidin-2-yl]cyclohexanecarboxylic acid, ethanolamine salt.
- 30 24. Pharmaceutical formulation according to Claims 16 to 23, in which the endothelin receptor antagonist is selected from the group consisting of bosentan, tezosentan and sitaxentan.

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25. Pharmaceutical formulation according to Claims 16 to 23, in which the endothelin receptor antagonist is selected from the group consisting of
- 5 a) BMS-193884 (EP 558258),
 b) BMS-207940 (Pharmaprojects (13.06.97)),
 c) BQ-123 (Exp.Opin.Invest.Drugs, 1997, 6, No.5, 475-487),
 d) SB-209670 (Exp.Opin.Invest.Drugs, 1997, 6, No.5, 475-487),
 e) SB-217242 (Exp.Opin.Invest.Drugs, 1997, 6, No.5, 475-487),
 f) SB-209598 (Trends in Pharmacol. Sci., 17, 177-81, 1996),
 10 g) TAK-044 (Exp.Opin.Invest.Drugs, 1997, 6, No.5, 475-487),
 h) Bosentan (Trends in Pharmacol. Sci., 18, 408-12, 1997),
 i) PD-156707 (J.Med.Chem., 40, No.7, 1063-74, 1997),
 j) L-749329 (Bioorg.Med.Chem.Lett., 7, No.3, 275-280, 1997),
 k) L-754142 (Exp.Opin.Invest.Drugs, 1997, 6, No.5, 475-487),
 15 l) ABT-627 (J.Med.Chem., 40, No.20, 3217-27, 1997),
 m) A-127772 (J.Med.Chem., 39, No.5, 1039-1048, 1996),
 n) A-206377 (213th American Chemical Society National Meeting, San Francisco, California, USA, 13 – 17 April 1997, Poster, MEDI 193),
 20 o) A-182086 (J.Med.Chem., 40, No.20, 3217-27, 1997),
 p) EMD-93246 (211th American Chemical Society National Meeting, New Orleans, USA, 1996, Poster, MEDI 143),
 q) EMD-122801 (Bioorg.Med.Chem.Lett., 8, No.1, 17-22, 1998),
 r) ZD-1611 (Trends in Pharmacol. Sci., 18, 408-12, 1997),
 25 s) AC-610612 (R&D Focus Drug News (18.05.98)),
 t) T-0201 (70th Annual Meeting of the Japanese Pharmacological Society, Chiba, Japan, 22-15 March 1997, Lecture, O-133),
 u) J-104132 (R&D Focus Drug News (15.12.97));

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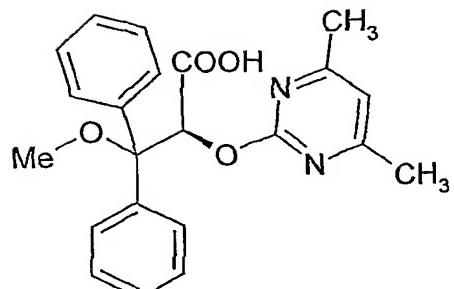


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v)

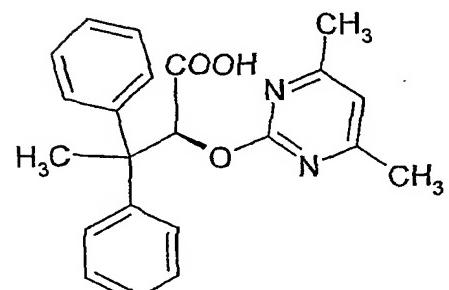
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w)

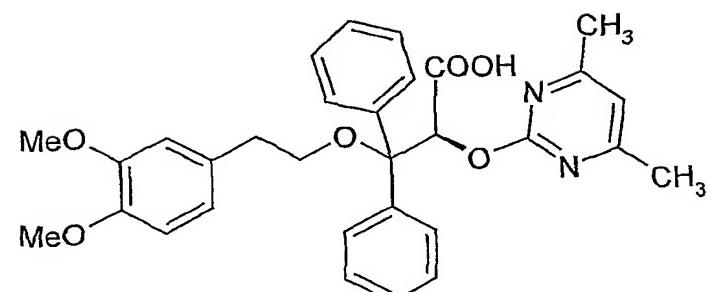
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x)

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y)

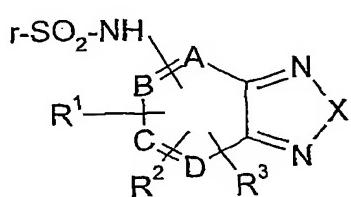
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26. Pharmaceutical formulation according to Claims 16 to 23, in which the endothelin receptor antagonist is selected from

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a) the compounds of the formula I described in EP 0733626

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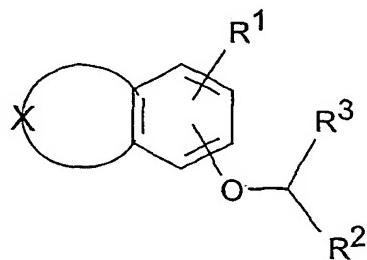
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in which

- A=B-C=D- is a -CH=CH-CH=CH- group in which 1 or 2 CH has
 (have) been replaced by N,
- 5 Ar is Ph or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by H, Hal, A, alkenyl having up to 6 carbon atoms, Ph, OPh, NO₂, NR⁴R⁵, NHCOR⁴, CF₃, OCF₃, CN, OR⁴, COOR⁴, (CH₂)_nCOOR⁴, (CH₂)_nNR⁴R⁵, -N=C=O or NHCONR⁴R⁵,
- 10 R¹, R²
 and R³ are each, independently of one another, absent, H, Hal, A, CF₃, NO₂, NR⁴R⁵, CN, COOR⁴, NHCOR⁴,
- R⁴ and R⁵ are each, independently of one another, H or A, or together are alternatively -CH₂-(CH₂)_n-CH₂-,
- 15 A is alkyl having from 1 to 6 carbon atoms,
- Ph is phenyl,
- X is O or S,
- Hal is F, Cl, Br or I,
- n is 1, 2 or 3,
- 20 and their salts, with the exception of 4-methyl-N-(2,1,3-benzothiadiazol-4-yl)benzenesulfonamide, 4-methyl-N-(2,1,3-benzothiadiazol-5-yl)benzenesulfonamide, 4-nitro-N-(2,1,3-benzothiadiazol-4-yl)benzenesulfonamide, 4-nitro-N-(2,1,3-benzothiadiazol-5-yl)benzenesulfonamide, 4-amino-N-(2,1,3-benzothiadiazol-4-yl)benzenesulfonamide and 4-amino-N-(2,1,3-benzothiadiazol-5-yl)benzenesulfonamide;
- 25

b) the compounds of the formula I described in EP 0733626

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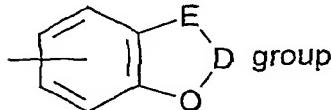


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in which

- 5 X is a saturated, partially unsaturated or completely unsaturated 3- to 4-membered alkylene chain, in which from 1 to 3 carbon atoms may be replaced by N and/or from 1 to 2 carbon atoms may be replaced by 1-2 O atoms and/or 1-2 S atoms, but where at most up to 3 carbon atoms may be replaced and where, in addition, a single, double or triple substitution of the alkylene chain and/or of a nitrogen located therein by A, R⁸ and/or NR⁴R⁴ may occur, and where furthermore one CH₂ group in the alkylene chain may also be replaced by a C=O group,
- 10 10 A is alkyl having 1-6 carbon atoms, in which one or two CH₂ groups may be replaced by O or S atoms or by -CR⁴=CR⁴- groups and in addition 1-7 H atoms may be replaced by F,
- 15 15 R¹ is H or A,
- 15 15 R² is COOR⁴, CN, 1H-tetrazol-5-yl or CONHSO₂R⁸,
- 20 20 R³ is Ar,
- 20 20 R⁴ and R⁴ are each, independently of one another, H, alkyl having from 1 to 6 carbon atoms or benzyl,
- 25 25 Ar is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R⁵, R⁶ or R⁷, or is a
- 30 30 which is unsubstituted or monosubstituted or disubstituted in the phenyl part by R⁵ or R⁶,
- 35 35 R⁵, R⁶
and R⁷ are each, independently of one another, R⁴, OR⁴, Hal, CF₃, OCF₃, OCHF₂, OCH₂F, NO₂, NR⁴R⁴, NHCOR⁴,



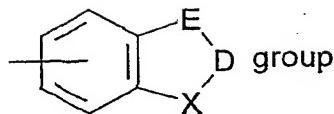
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- CN, NHSO_2R^4 , COOR^4 , COR^4 , $\text{CONHSO}_2\text{R}^8$, $\text{O}(\text{CH}_2)_n\text{R}^2$,
 OPh , $\text{O}(\text{CH}_2)_n\text{OR}^4$ or $\text{S}(\text{O})_m\text{R}^4$,
- 5 R^8 is phenyl or naphthyl, each of which is unsubstituted or
 monosubstituted, disubstituted or trisubstituted by A,
 OR^1 , NR^4R^4 or Hal,
- 10 E is CH_2 or O,
 D is carbonyl or $[\text{C}(\text{R}^4\text{R}^4)]_n$,
 Hal is F, Cl, Br or I,
 m is 0, 1 or 2,
 n is 1 or 2,
 and their salts;

c) the compounds of the formula I described in EP 0755934

- 15 I
-
- 20 in which
- Y-Z- is $-\text{NR}^7\text{-CO-}$, $-\text{N=C(OR}^7\text{)-}$ or $-\text{N=CR}^8\text{-}$,
 R¹ is Ar,
 R² is COOR^6 , CN, 1H-tetrazol-5-yl or CONHSO_2Ar ,
 R³, R⁴
 and R⁵ are each, independently of one another, R⁶, OR⁶, S(O)_mR⁶, Hal, NO₂, NR⁶R⁶, NHCOR⁶, NHSO₂R⁶, OCOR⁶, COOR⁶ or CN,
 R⁶ and R⁶ are each, independently of one another, H, alkyl having
 from 1 to 6 carbon atoms, benzyl or phenyl,
 R⁷ is $(\text{CH}_2)_n\text{Ar}$,
 R⁸ is Ar or OAr,
 Ar is phenyl which is unsubstituted or monosubstituted,
 disubstituted or trisubstituted by R⁹, R¹⁰ or R¹¹, or is
 unsubstituted naphthyl or a

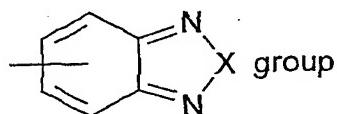
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which is unsubstituted or monosubstituted or disubstituted in the phenyl part by R⁹ or R¹⁰, or is
a

10



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which is unsubstituted or monosubstituted or disubstituted in the cyclohexadienyl part by R⁹ or R¹⁰,

20

R⁹, R¹⁰
and R¹¹ are each, independently of one another, R⁶, OR⁶, Hal,
CF₃, OCF₃, OCHF₂, OCH₂F, NO₂, NR⁶R⁶, NHCOR⁶, CN,
NHSO₂R⁶, COOR⁶, COR⁶, CONHSO₂Ar, O(CH₂)_nR²,

O(CH₂)_nOR⁶ or S(O)_mR⁶,

E is CH₂, S or O,

D is carbonyl or [C(R⁶R⁶)]_n,

Hal is F, Cl, Br or I,

X is O or S,

m is 0, 1 or 2,

n is 1 or 2,

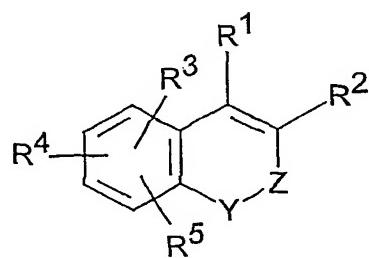
and their salts;

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d) the compounds of the formula I described in EP 0757039

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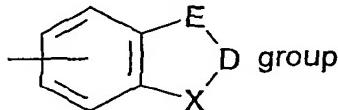
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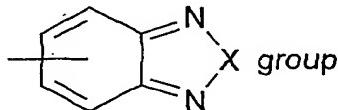
I

in which

- 5 -Y-Z- is -NR⁷-CO-, -N=C(OR⁷)- or -N=CR⁸-,
 R¹ is Ar,
 R² is COOR⁶, (CH₂)_nCOOR⁶, CN, 1H-tetrazol-5-yl or
 CONHSO₂Ar,
 R³, R⁴
 and R⁵ are each, independently of one another, R⁶, OR⁶,
 S(O)_mR⁶, Hal, NO₂, NR⁶R^{6'}, NHCOR⁶, NHSO₂R⁶,
 OCOR⁶, COR⁶, COOR⁶ or CN, where R³ and R⁴
 together may alternatively be an O(CH₂)_nO group,
 10 R⁶ and R^{6'} are each, independently of one another, H, alkyl having
 from 1 to 6 carbon atoms, benzyl or phenyl,
 R⁷ is (CH₂)_nAr,
 R⁸ is Ar or OAr,
 15 Ar is phenyl which is unsubstituted or monosubstituted,
 disubstituted or trisubstituted by R⁹, R¹⁰ or R¹¹, or is
 unsubstituted naphthyl or a



which is unsubstituted or monosubstituted or
 disubstituted in the phenyl part by R⁹ or R¹⁰, or is
 a



30 which is unsubstituted or monosubstituted or disubsti-
 tuted in the cyclohexadienyl part by R⁹ or R¹⁰,

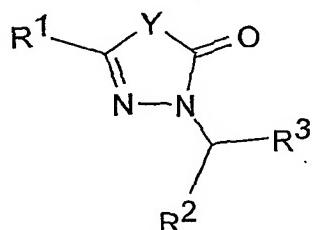
- R⁹, R¹⁰
 and R¹¹ are each, independently of one another, R⁶, OR⁶, Hal,
 CF₃, OCF₃, OCH₂F, OCH₂F, NO₂, NR⁶R^{6'}, NHCOR⁶, CN,

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NHSO₂R⁶, COOR⁶, COR⁶, CONHSO₂Ar, O(CH₂)_nR²,
 O(CH₂)_nOR⁶ or S(O)_mR⁶,

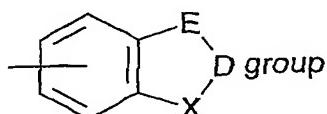
- 5 E is CH₂, S or O,
 D is carbonyl or [C(R⁶R⁶')]_n,
 X is O or S,
 Hal is F, Cl, Br or I,
 m is 0, 1 or 2,
 n is 1 or 2,
 and their salts;

10 e) the compounds of the formula I described in EP 0796250

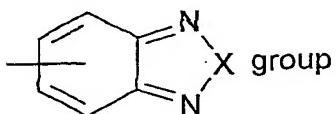


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- in which
 20 Y is -C(R⁴R⁴)-C(R⁴R⁴)-, -CR⁴=CR⁴- or -C(R⁴R⁴)-S-,
 R¹ is Het, Ar, R³ or R⁴,
 R² is Ar or a



which is unsubstituted or monosubstituted or disubstituted in the phenyl part by A, R³, OR⁴, NH₂, NHA, NA₂, NO₂, CN, Hal, NHCOR⁴, NHSO₂R⁴, COOR⁴, COR⁴, CONHSO₂R⁶, O(CH₂)_nR³, OPh, O(CH₂)_nOR⁴ or S(O)_mR⁴,
 30 or a



which is unsubstituted or monosubstituted or disubstituted in the cyclohexadienyl part by A, R³, OR⁴, NH₂, NHA, NA₂, NO₂, CN, Hal, NHCOR⁴, NHSO₂R⁴, COOR⁴, COR⁴, CONHSO₂R⁶, O(CH₂)_nR³, OPh, O(CH₂)_nOR⁴ or S(O)_mR⁴,

5 R³ is CN, COOH, COOA, CONHSO₂R⁵ or 1H-tetrazol-5-yl,

 R⁴ and R⁴ are each, independently of one another, H, A, or phenyl or benzyl, each of which is unsubstituted or monosubstituted by alkoxy,

10 R⁵ is A or Ar,

 R⁶ is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR⁵, NH₂, NHA, NA₂, NO₂, CN or Hal,

15 A is alkyl having 1-6 carbon atoms, in which one or two CH₂ groups may be replaced by O or S atoms or by -CR⁴=CR⁴- groups and in addition 1-7 H atoms may be replaced by F, or benzyl,

20 Ar is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR⁴, NH₂, NHA, NA₂, NO₂, CN, Hal, NHCOR⁴, NHSO₂R⁴, COOR⁴, COR⁴, CONHSO₂R⁶, O(CH₂)_nR³, OPh, O(CH₂)_nOR⁴ or S(O)_mR⁴,

25 Het is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/or S atoms, bonded via N or C, which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, R³, NH₂, NHA, NA₂, CN, NO₂

30 D and/or carbonyl oxygen,

 E is carbonyl or [C(R⁴R⁴)]_n,

 Hal is CH₂, S or O,

 X is F, Cl, Br or I,

 m is O or S,

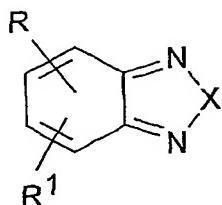
35 n is 0, 1 or 2,

 n is 1 or 2,

and their salts;

f) the compounds of the formula I described in WO 9719077

5



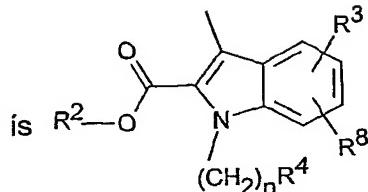
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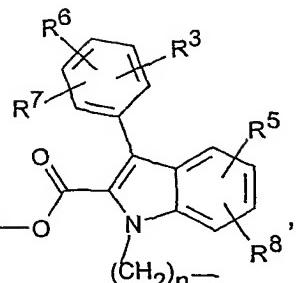
in which

15

R



or



20

X

is O or S,

R¹

is H, Hal, OH, OA, A, alkylene-O-A, NO₂, NH₂, NH-acyl, SO₂NH₂, SO₃-A, SO₂NHA, CN or formyl,

R²

is H or A,

R³, R⁵, R⁶

are each, independently of one another, H, Hal, OH,

OA, O-alkylene-R⁴, A, S-A, NO₂, NH₂, NHA, NA₂,

NH-acyl, NHSO₂A, NHSO₂R⁴, NASO₂A, NASO₂-R⁴,

NH(CO)NH₂, NH(CO)NHA, formyl, NH(CO)NH-phenyl,

NHCOOA, NA-acyl, NHR⁴, NHCOOR⁴, NHCOO-benzyl,

NHSO₂-benzyl, NHCOO-alkylene-OA, NH(CO)NA₂,

N-piperidinyl-CO-NH, N-pyrrolidinyl-CONH,

O(CH₂)_nCOOR², O(CH₂)_nOR², CH₂OH or CH₂OA,

R³ and R⁶

together are alternatively -O-CH₂-O-, -O-CH₂-CH₂-O-,
-O-CH₂-CH₂-O-, -O-CF₂-O- or -O-CF₂-CF₂-O-,

R⁴

is phenyl which is unsubstituted or monosubstituted or
polysubstituted by R³ and/or R⁶,

35

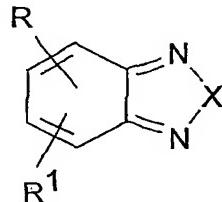
A

is alkyl having 1-6 carbon atoms,

Hal is fluorine, chlorine, bromine or iodine,
 n is 1 or 2,
 and their salts;

5 g) the compounds of the formula I described in WO 9730982

10

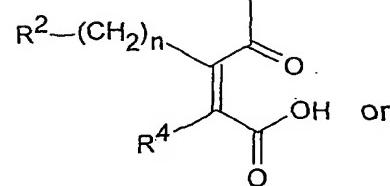
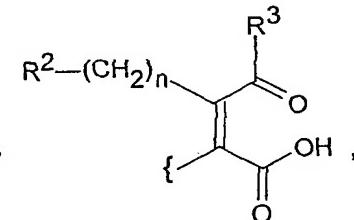


I

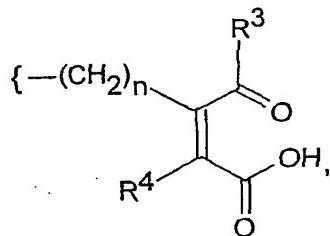
in which

15

R



20



25

X is O or S,

R¹ is H, Hal, OH, OA, A, alkylene-O-A, NO₂, NH₂, NH-acyl, SO₂NH₂, SO₃-A, SO₂NHA, CN or formyl,

30

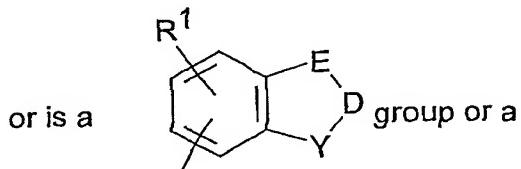
R², R³ and R⁴ are each, independently of one another, a phenyl group which is unsubstituted or monosubstituted or polysubstituted by Hal, OH, OA, O-alkylene-R⁵, A, S-A, SOA, SO₂A, SOR⁵, SO₂R⁵, NO₂, NH₂, NHA, NA₂, NH-acyl, NHSO₂A, NHSO₂R⁵, NASO₂A, NASO₂-R⁵, NH(CO)NH₂, NH(CO)NHA, formyl, NH(CO)NHR⁵, NHCOOA, NA-acyl, NHCOOCH₂R⁵, NHSO₂CH₂R⁵, NHCOO-alkylene-OA, NH(CO)NA₂, 1-piperidinyl-CO-NH, 1-pyrrolidinyl-CONH,

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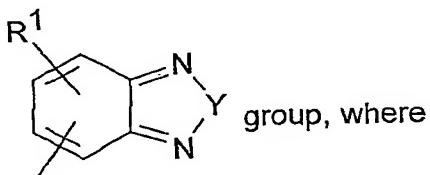
- 149 -

$O(CH_2)_nCOOA$, $O(CH_2)_nCOOH$, $O(CH_2)_nOH$, $O(CH_2)_nOA$,
 CH_2OH , CH_2OA , $COOH$, $COOA$, CH_2COOH or
 CH_2COOA ,

5



10



R^2 is additionally A or cycloalkyl,

15

R^5 is a phenyl group which is unsubstituted or monosubstituted or polysubstituted by Hal, OH, OA, A, S-A, NO_2 , NH_2 , NHA , NA_2 , NH-acyl, $NHSO_2A$, $NASO_2A$, $NH(CO)NH_2$, $NH(CO)NHA$, formyl, $NHCOOA$, NA -acyl, $NHCOO$ -alkylene-OA, $NH(CO)NA_2$, N-piperidinyl-CO-

20

NH , N-pyrrolidinyl-CONH, $O(CH_2)_nCOOA$, $O(CH_2)_nCOOH$, $O(CH_2)_nOH$, $O(CH_2)_nOA$, CH_2OH , CH_2OA , $COOH$, $COOA$, CH_2COOH or CH_2COOA ,

A is alkyl having 1-6 carbon atoms, in which one or two CH_2 groups may be replaced by O or S atoms or by $-CR^6=CR^6-$ groups and/or 1-7 H atoms may be replaced by F,

D is carbonyl or $[C(R^6R^6')]_m$,

E is CH_2 , S or O,

Y is O or S,

30

R^6 and $R^{6'}$ are each, independently of one another, H, F or A,

Hal is fluorine, chlorine, bromine or iodine,

n is 1 or 2, and

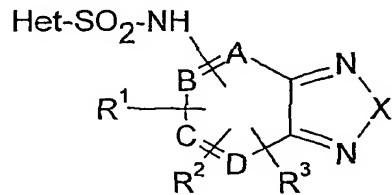
m is 1 or 2,

or a tautomeric cyclised form, and the (E)-isomers and the salts of all isomers;

35

- 150 -

h) the compounds of the formula I described in WO 9730996



I

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in which

10

-A=B-C=D- is a -CH=CH-CH=CH- group, in which, in addition, 1 or 2 CH may be replaced by N,

Het is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/or S atoms which is unsubstituted or substituted by -Z-R⁶,

15

R¹, R² and R³ are each, independently of one another, absent, H, Hal, A, CF₃, NO₂, NR⁴R⁵, CN, COOR⁴ or NHCOR⁴,

R⁴ and R⁵ are each, independently of one another, H or A, or together are alternatively -CH₂-(CH₂)ₙ-CH₂-,

20

R⁶ is a phenyl radical, benzothiadiazol-5-yl or benzoxadiazol-5-yl radical, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R⁷, R⁸ and/or R⁹,

25

R⁷, R⁸ and R⁹ are each, independently of one another, A, O-A, CN, COOH, COOA, Hal, formyl, -CO-A, and R⁷ and R⁸ are alternatively -O-(CH₂)ₘ-O-,

A is alkyl having from 1 to 6 carbon atoms,

X is O or S,

30

Z is -CO-, -CONH-, -CO-(CH₂)ₙ-, -CH=CH-, -(CH₂)ₙ-, -CONHCO-, -NHCONH-, -NHCOO-, -O-CONH-, -CO-O- or -O-CO-,

Hal is F, Cl, Br or I,

m is 1 or 2, and

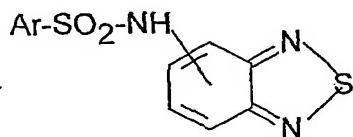
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n is 1, 2 or 3,

and their salts;

- 151 -

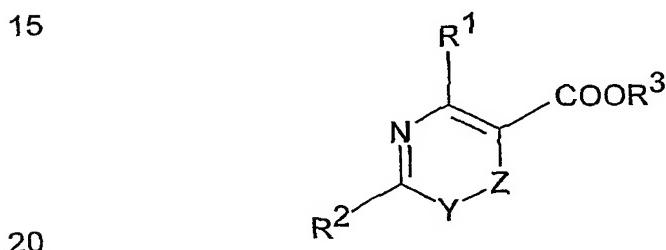
i) the compounds of the formula I described in DE 19609597



in which

Ar is naphthyl which is monosubstituted by NH₂, NHA or
NA₂, and10 A is alkyl having from 1 to 6 carbon atoms,
and their physiologically acceptable salts;

j) the compounds of the formula I described in DE 19612101

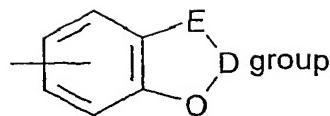


in which

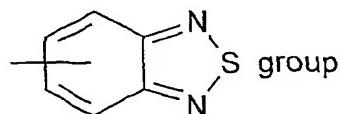
-Y-Z- is -NR⁴-CO or -N=CR⁵-,R¹ is Ar,25 R² is H, alkyl having 1-6 carbon atoms which is unsubstituted or monosubstituted, disubstituted or trisubstituted by OR³ or Hal, or (CH₂)_mPh or (CH₂)_m-cycloalkyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R³, OR³ or Hal,30 R³ and R^{3'} are each, independently of one another, H, alkyl having 1-6 carbon atoms or benzyl,R⁴ is CH₂Ar,R⁵ is OCH₂Ar,Ar is phenyl which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R⁶, R⁷ or R⁸, or a

35

- 152 -



which is unsubstituted or monosubstituted in the phenyl part by R⁶, or a



10

which is unsubstituted or monosubstituted in the cyclohexadienyl part by R⁶,

E is CH₂ or O,

D is carbonyl or (CH₂)_n,

15 E and D together are alternatively CH=CR⁹,

R⁶, R⁵ are each, independently of one another, R³, OR³ or Hal,

R⁷ is R³, OR³, Hal, NO₂, NH₂, NHR³, NR³R³, NHCOR³, COOR³, O(CH₂)_nR³ or O(CH₂)_nOR³,

R⁸ is Ph which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R³, OR³, Hal, NO₂, NH₂,

NHR⁶, NR⁶R⁶, NHCOR³ or COOR³,

R⁹ is H, OH, CH₂OH or COOR³,

Hal is F, Cl, Br or I,

Ph is phenyl,

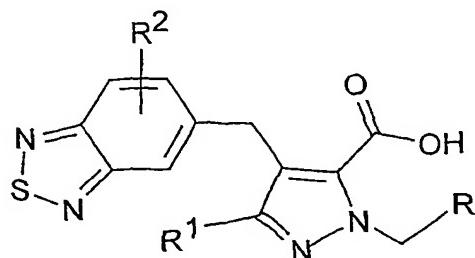
25 m is 0 or 1,

n is 1 or 2,

and their salts;

k) the compounds of the formula I described in WO 9827091

30



35

- 153 -

in which

5 R is phenyl which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R³, R⁴ or R⁵, or 2,1,3-benzothiadiazolyl which is unsubstituted or mono-substituted by R²,

10 R¹ is A, in which 1-7 H atoms may be replaced by F, is -S-A, -O-A, is phenyl or -alkylene-phenyl, each of which is unsubstituted or monosubstituted by R³, or is thienyl which is unsubstituted or monosubstituted by R³,

15 R² is A, F, Cl, Br or -O-A,

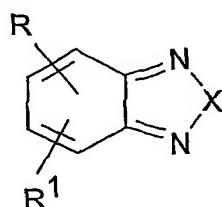
R³, R⁴
and R⁵ are each, independently of one another, A, -O-A, -S-A, -O-alkylene-COOH, -alkylene-COOH or COOH,

R³ and R⁴ together are alternatively -O-CH₂-O-, and

15 A is alkyl having 1-7 carbon atoms,
and their salts;

I) the compounds of the formula I described in WO 9827077

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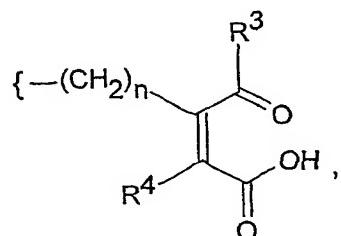
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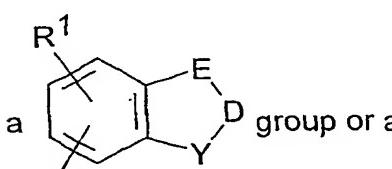
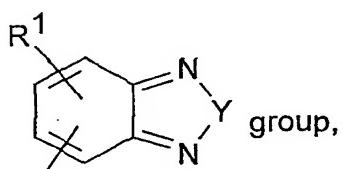
25

in which

R is

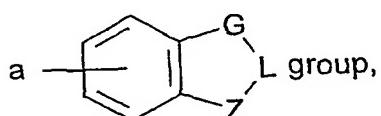
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- X is O or S,
 R¹ is H, Hal, OH, OA, A, alkylene-O-A, NO₂, NH₂, NH-acyl, SO₂NH₂, SO₃-A, SO₂NHA, CN or formyl,
 R², R³
 5 and R⁴ are each, independently of one another, a phenyl group which is unsubstituted or monosubstituted or polysubstituted by R⁷, where R² is additionally A or cycloalkyl, or are
- 10 
- 15 
- 20 with the proviso that at least one of the radicals R², R³ or R⁴ is an R⁸ radical which is unsubstituted or monosubstituted or polysubstituted by R⁷,
- R⁵ is a phenyl group which is unsubstituted or monosubstituted or polysubstituted by Hal, OH, OA, A, S-A, NO₂, NH₂, NHA, NA₂, NH-acyl, NSO₂A, NASO₂A, NH(CO)NH₂, NH(CO)NHA, formyl, NHCOOA, NA-acyl, NHCOO-alkylene-OA, NH(CO)NA₂, N-piperidinyl-CO-NH, N-pyrrolidinyl-CONH, O(CH₂)_nCOOA, O(CH₂)_nCOOH, O(CH₂)_nOH, O(CH₂)_nOA, CH₂OH, CH₂OA, COOH, COOA, CH₂COOH or CH₂COOA,
- 25 A is alkyl having 1-6 carbon atoms, in which one or two CH₂ groups may be replaced by O or S atoms or by -CR⁶=CR⁶- groups and/or 1-7 H atoms may be replaced by F,
- 30 D is carbonyl or [C(R⁶R⁶)]_m,
 E is CH₂, S or O,
- 35

Y is O or S,
 R⁶ and R^{6'} are each, independently of one another, H, F or A,
 R⁷ is Hal, OH, OA, O-alkylene-R⁵, A, S-A, S-OA, SO₂A,
 S-OR⁵, SO₂R⁵, NO₂, NH₂, NHA, NA₂, NH-acyl, NSO₂A,
 5 NHSO₂R⁵, NASO₂A, NASO₂-R⁵, NH(CO)NH₂,
 NH(CO)NHA, formyl, NH(CO)NHR⁵, NHCOOA, NA-acyl,
 NHCOOCH₂R⁵, NHSO₂CH₂R⁵, NHCOO-alkylene-OA,
 NH(CO)NA₂, 1-piperidinyl-CO-NH, 1-pyrrolidinyl-CONH,
 O(CH₂)_nCOOA, O(CH₂)_nCOOH, O(CH₂)_nOH, O(CH₂)_nOA,
 10 CH₂OH, CH₂OA, COOH, COOA, CH₂COOH or
 CH₂COOA,
 R⁸ is a 5-7-membered heterocyclic radical having 1-4 N, O
 and/or S atoms or is

15



20

G and Z are each, independently of one another, -CH=, N, O or
 S,

L is -CH=, -CH=CH- or -CH₂-CH₂-CH₂-,

Hal is fluorine, chlorine, bromine or iodine,

n is 0, 1 or 2, and

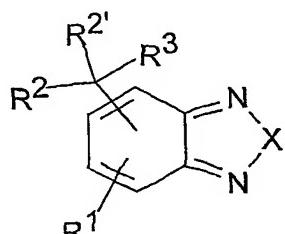
m is 1 or 2,

25

or a tautomeric cyclised form, and the (E)-isomers and the salts of all
 isomers;

m) the compounds of the formula I described in WO 9841515

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35

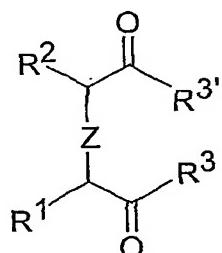
	in which	
	X	is O or S,
5	R ¹	is H, Hal, OH, OA, A, NO ₂ , NH ₂ , NHA, NAA', NHCOR ⁴ , NHCOR ⁶ , NHSO ₂ R ⁴ , NHSO ₂ R ⁶ , S(O) _m R ⁶ , SO ₃ H, SO ₂ NR ⁴ R ⁴ ' or formyl,
	R ² and R ^{2'}	are each, independently of one another, A, (CH ₂) _n Ar, (CH ₂) _n Het, CH ₂ COAr, CH ₂ COHet or OAr,
10	R ^{2'}	is additionally also H,
	R ³	is COOR ⁴ , CN, 1H-tetrazol-5-yl or CONHSO ₂ R ⁵ ,
15	R ⁴ and R ^{4'}	are each, independently of one another, H or A,
	R ⁵	is A or Ar,
	R ⁶	is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, NH ₂ , NHA, NAA', NO ₂ , CN or Hal,
20	R ⁷ and R ^{7'}	are each, independently of one another, H or alkyl having 1-6 carbon atoms,
	A and A'	are each, independently of one another, alkyl having 1-6 carbon atoms, in which one or two CH ₂ groups may be replaced by O or S atoms or by -CR ⁷ =CR ⁷ - groups and/or 1-7 H atoms may be replaced by F, or benzyl,
25	Ar	is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR ⁴ , NH ₂ , NHA, NAA', NO ₂ , CN, Hal, NHCOR ⁴ , NHCOR ⁶ , NHSO ₂ R ⁴ , NHSO ₂ R ⁶ , COOR ⁴ , OPh, CONH ₂ , CONHA, CONAA', COR ⁴ , CONHSO ₂ R ⁴ , CONHSO ₂ R ⁶ , O(CH ₂) _n COOR ⁴ , O(CH ₂) _n OR ⁴ , SO ₃ H, SO ₂ NR ⁴ R ⁴ ', S(O) _m R ⁶ or S(O) _m R ⁴ ,
30	Het	is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having 1-4 N, O and/or S atoms, bonded via N or C, which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, R ³ , NH ₂ , NHA, NAA', NO ₂ and/or =O,
	Hal	is fluorine, chlorine, bromine or iodine,
35	m	is 0, 1 or 2, and
	n	is 1 or 2,

- 157 -

where, if R^2 is CH_2COAr and R^2 is H, R^3 is not $COOA$,
and salts thereof;

n) the compounds of the formula I described in WO 9841521

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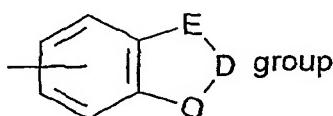
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in which

Z is a single or double bond,

R1 is a

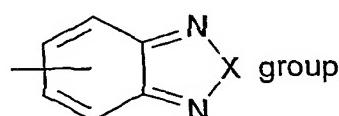
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20

which is unsubstituted or monosubstituted in the phenyl part by R^7 , or is a

25



which is unsubstituted or monosubstituted in the cyclohexadienyl part by R^7 ,

30 R^2 is A, Ar-(CH_2) $_m$, cycloalkyl-(CH_2) $_m$, Het-(CH_2) $_m$ or R^1 -(CH_2) $_m$,
 R^3 and $R^{3'}$ are each, independently of one another, OR 4 , $NHSO_2R^5$,
 NH_2 , NHA or NAA',

R^3 and $R^{3'}$ together are alternatively -O-, forming a cyclic anhydride,
 R^4 and $R^{4'}$ are each, independently of one another, H or A,

R^5 is A or Ar,

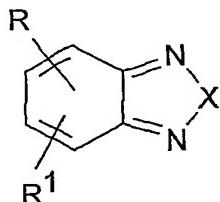
35

R⁶ is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, NH₂, NHA, NAA', NO₂, CN or Hal,
 5 R⁷ is A, COOR⁴, CN, 1H-tetrazol-5-yl, CONHSO₂R⁵, Hal, OR⁴, NO₂, NH₂, NHA, NAA', NHCOR⁴, NHCOR⁶, NHSO₂R⁴, NHSO₂R⁶, S(O)_kR⁴, S(O)_kR⁶, SO₂NR⁴R⁴ or formyl,
 R⁸ and R^{8'} are each, independently of one another, H or alkyl having 1-6 carbon atoms,
 10 E is CH₂ or O,
 D is carbonyl or (CR⁴R⁴)_n,
 E and D together are alternatively CR⁴=R⁴',
 X is S or O,
 A and A' are each, independently of one another, alkyl having 1-6 carbon atoms, in which one or two CH₂ groups may be replaced by O or S atoms or by -CR⁸=CR^{8'}- groups and/or
 15 1-7 H atoms may be replaced by F, or benzyl,
 Ar is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR⁴, NH₂, NHA, NAA', NO₂, CN, Hal, NHCOR⁴, NHCOR⁶, NHSO₂R⁴, NHSO₂R⁶, COOR⁴, OPh, CONH₂, CONHA, CONAA', COR⁴, CONHSO₂R⁴, CONHSO₂R⁶, O(CH₂)_nCOOR⁴, O(CH₂)_nOR⁴, SO₂NR⁴R⁴, S(O)_kR⁶ or S(O)_kR⁴,
 20 Het is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having 1-4 N, O and/or S atoms, bonded via N or C, which may be unsubstituted, monosubstituted or disubstituted or trisubstituted by Hal, A, COOR⁴, CN, 1H-tetrazol-5-yl, CONHSO₂R⁵, NH₂, NHA,
 25 NAA', NO₂ and/or =O,
 Hal is fluorine, chlorine, bromine or iodine,
 k is 0, 1 or 2,
 m is 0, 1 or 2, and
 n is 1 or 2,
 30 35 and the (Z)- and (E)-isomers and the salts of all isomers;

- 159 -

o) the compounds of the formula I described in WO 9842702

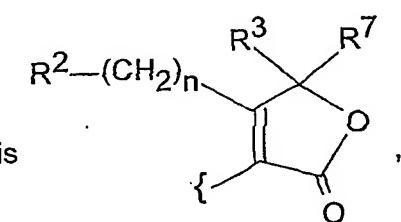
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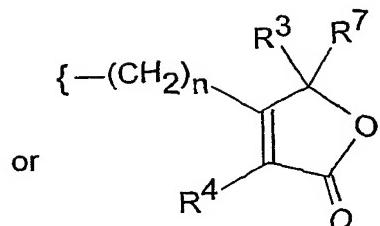
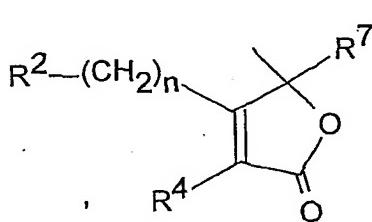
10

in which

R



15



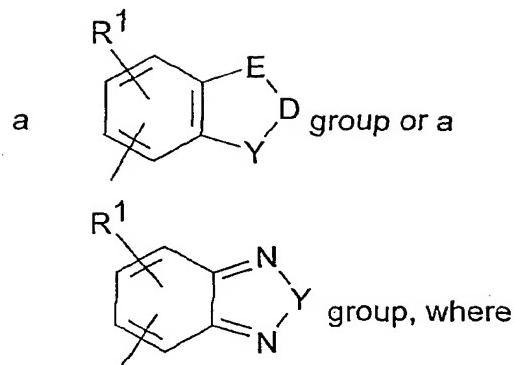
20

X and Y are each, independently of one another, O or S,
 R¹ is H, Hal, OH, OA, A, alkylene-O-A, NO₂, NH₂, NH-acyl,
 SO₂NH₂, SO₂-A, SO₂NHA, CN or formyl,

25

R², R³ and R⁴ are each, independently of one another, a phenyl group which is unsubstituted or monosubstituted or polysubstituted by Hal, OH, OA, O-alkylene-R⁵, A, S-A, S-OA, SO₂A, S-OR⁵, SO₂R⁵, NO₂, NH₂, NHA, NA₂, NH-acyl, NHSO₂A, NHSO₂R⁵, NASO₂A, NASO₂-R⁵, NH(CO)NH₂, NH(CO)NHA, formyl, NH(CO)NHR⁵, NHCOOA, NA-acyl, NHCOOCH₂R⁵, NHSO₂CH₂R⁵, NHCOO-alkylene-OA, NH(CO)NA₂, 1-piperidinyl-CO-NH, 1-pyrrolidinyl-CONH, O(CH₂)_nCOOA, O(CH₂)_nCOOH, O(CH₂)_nOH, O(CH₂)_nOA, CH₂OH, CH₂OA, COOH, COOA, CH₂COOH or CH₂COOA,

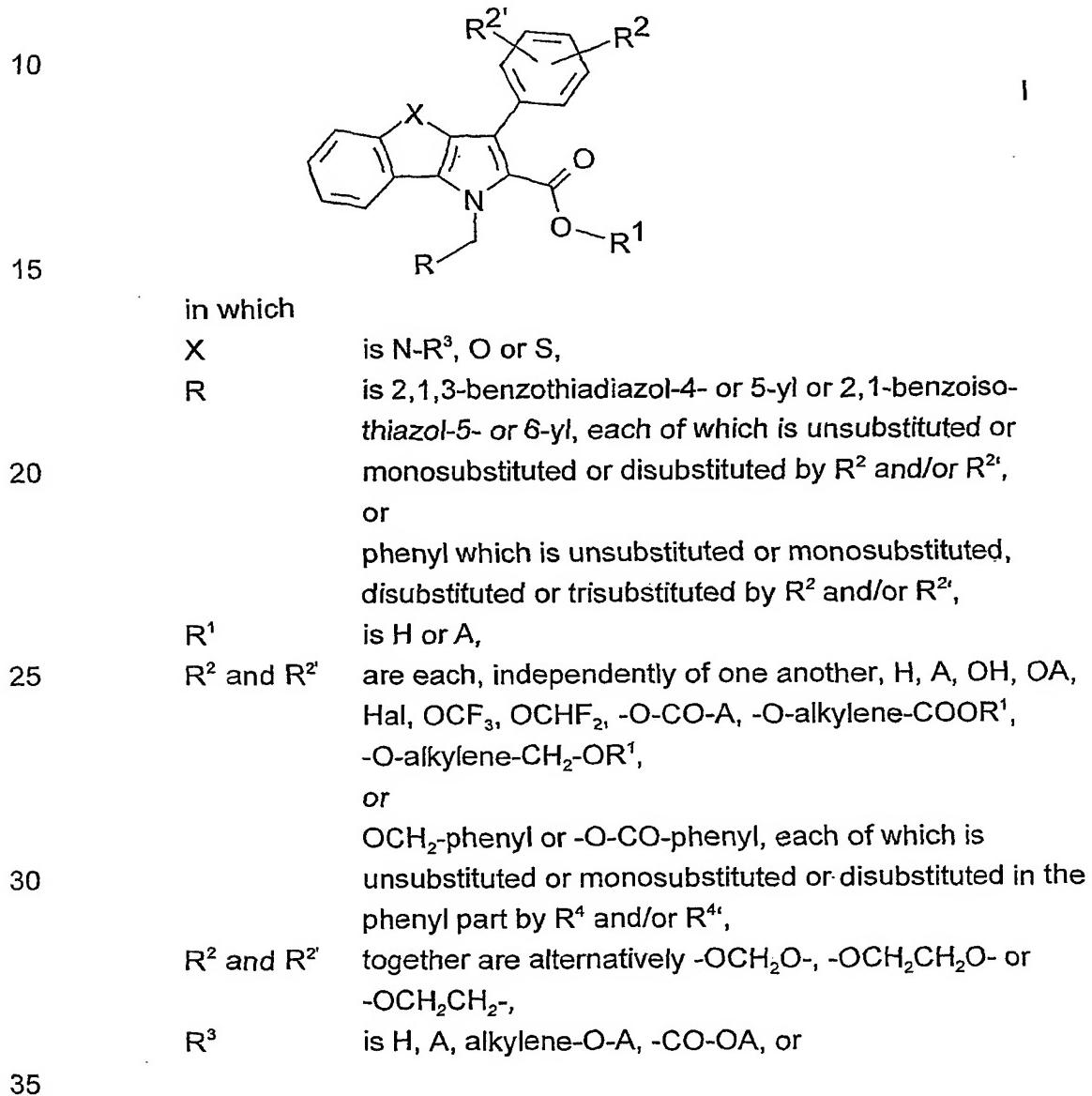
- 160 -



- 161 -

or is naphthyl, A-O-C(=O)- or Hal,
 Hal is fluorine, chlorine, bromine or iodine,
 n is 0, 1 or 2, and
 m is 1 or 2,
 5 and salts thereof;

p) the compounds of the formula I described in WO 9842709



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alkylene-phenyl which is unsubstituted or mono-substituted or disubstituted in the phenyl part by R⁴ and/or R^{4'},

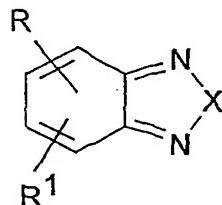
5 R⁴ and R^{4'} are each, independently of one another, H, A, OH, OA, Hal, COOR¹ or CH₂OR¹,

A is alkyl having 1-6 carbon atoms,

Hal is fluorine, chlorine, bromine or iodine, and their salts;

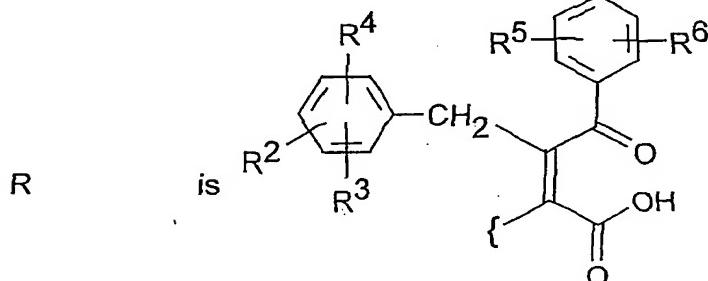
10 q) the compounds of the formula I described in WO 9905132

15



in which

20



25

30

X is O or S,

R¹ is H, Hal, OA or A,

R², R³, R⁵, and R⁶ are each, independently of one another, H, Hal, A, OA or R⁴,

R⁴ is -O-(CH₂)_n-Cy,

Cy is cycloalkyl having 3-8 carbon atoms,

35 A is alkyl having 1-6 carbon atoms, in which one or two CH₂ groups may be replaced by O or S atoms or by

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-CR⁵=CR^{5'}- groups and/or 1-7 H atoms may be replaced by F,

R⁵ and R^{5'} are each, independently of one another, H, F or A,

Hal is fluorine, chlorine, bromine or iodine,

5 n is 0, 1 or 2,

or a tautomeric cyclised form, and the (E)-isomers and the salts of all isomers.

27. Pharmaceutical formulation according to one of the preceding claims,
10 comprising one or more excipients and/or assistants.

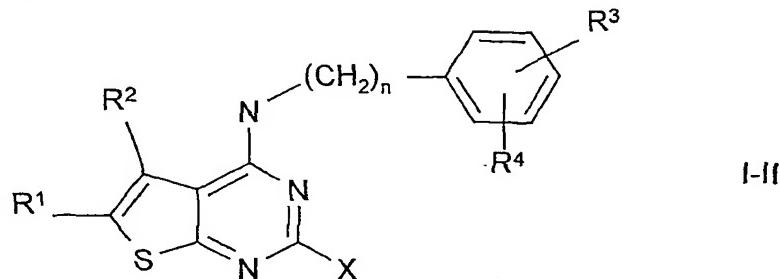
28. Use of a pharmaceutical preparation according to one of Claims 16 to
15 27 for the preparation of a medicament for the treatment of angina,
high blood pressure, high pulmonary pressure, congestive heart
failure (CHF), chronic obstructive pulmonary disease (COPD), cor
pulmonale, dextrocardiac insufficiency, atherosclerosis, conditions of
reduced patency of the heart vessels, peripheral vascular diseases,
strokes, bronchitis, allergic asthma, chronic asthma, allergic rhinitis,
20 glaucoma, irritable bowel syndrome, tumours, renal insufficiency, liver
cirrhosis, erectile dysfunction and for the treatment of female sexual
disorders.

29. Use according to Claim 28 for the preparation of a medicament for
the treatment of high pulmonary pressure, congestive heart failure
25 (CHF), chronic obstructive pulmonary disease (COPD), cor pulmo-
nale and/or dextrocardiac insufficiency.

30. Set (kit) consisting of separate packs of
(a) an effective amount of 4-[4-(3-chloro-4-methoxybenzyl-
amino)benzothieno[2,3-d]pyrimidin-2-yl]cyclohexanecarboxylic acid
and/or physiologically acceptable salts and/or solvates thereof
and
(b) an effective amount of an endothelin receptor antagonist.

31. Pharmaceutical formulation comprising at least one compound of the formula I-II

5



10

in which

R¹ and R² are each, independently of one another, H, A or Hal, where one of the radicals R¹ or R² is always ≠ H,

15

R¹ and R² together are alternatively alkylene having 3-5 carbon atoms,

R³ and R⁴ are each, independently of one another, H, A, OH, OA or Hal,

20

R³ and R⁴ together are alternatively alkylene having 3-5 carbon atoms, -O-CH₂-CH₂-, -O-CH₂-O- or -O-CH₂-CH₂-O-,

X is R⁵ or R⁶, each of which is monosubstituted by R⁷,

25

R⁵ is linear or branched alkylene having 1-10 carbon atoms, in which one or two CH₂ groups may be replaced by -CH=CH- groups, or

-C₆H₄-(CH₂)_m-,

R⁶ is cycloalkylalkylene having 6-12 carbon atoms,

R⁷ is COOH, COOA, CONH₂, CONHA, CON(A)₂ or CN,

A is alkyl having from 1 to 6 carbon atoms,

Hal is F, Cl, Br or I,

30

m is 1 or 2, and

n is 0, 1, 2 or 3,

and/or physiologically acceptable salts and/or solvates thereof and at least one endothelin receptor antagonist.

35

32. Pharmaceutical formulation according to Claim 31, comprising at least one compound of the formula I-II according to Claim 31 in which

X is R⁵ or R⁶, each of which is substituted by COOH or COOA.

33. Pharmaceutical formulation according to Claim 31, comprising at least one compound of the formula I-II according to Claim 31 in which

5 R¹ and R² are each, independently of one another, H, A or Hal, where at least one of the radicals R¹ and R² is always ≠ H,
R³ and R⁴ together are alkylene having 3-5 carbon atoms, -O-CH₂-CH₂- , -O-CH₂-O- or -O-CH₂-CH₂-O,
10 X is R⁵ or R⁶, each of which is substituted by COOH or COOA.

34. Pharmaceutical formulation according to Claim 31, comprising at least one compound of the formula I-II according to Claim 31 in which

15 R¹ and R² are each, independently of one another, H, A or Hal, where at least one of the radicals R¹ and R² is always ≠ H,
R³ and R⁴ are each, independently of one another, H, A, OA or Hal,
20 R³ and R⁴ together are alkylene having 3-5 carbon atoms, -O-CH₂-CH₂- , -O-CH₂-O- or -O-CH₂-CH₂-O,
X is R⁵ or R⁶, each of which is substituted by COOH or COOA,
n is 1 or 2.

25 35. Pharmaceutical formulation according to Claim 31, comprising at least one compound of the formula I-II according to Claim 31 in which
R¹ and R² are each, independently of one another, H, A or Hal, where one of the radicals R¹ and R² is always ≠ H,
30 R¹ and R² together are alternatively alkylene having 3-5 carbon atoms,
R³ and R⁴ are each, independently of one another, H, A, OA or Hal,
R³ and R⁴ together are alternatively -O-CH₂-O-,
35 X is R⁵ which is monosubstituted by R⁷,

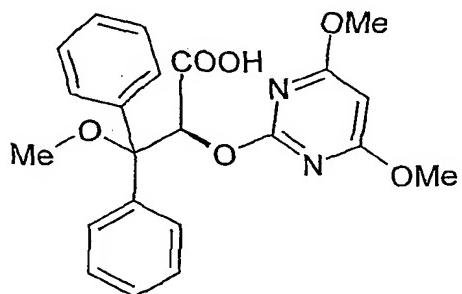
- R⁵ is linear or branched alkylene having 1-10 carbon atoms, or
 -C₆H₄-CH₂-,
- R⁷ is COOH or COOA,
- 5 A is alkyl having from 1 to 6 carbon atoms,
- Hal is F, Cl, Br or I,
- m is 1, and
- n is 1 or 2.
- 10 36. Pharmaceutical formulation according to Claim 31, comprising at least one compound of the formula I-II according to Claim 31 in which R¹ and R² are each, independently of one another, H, A or Hal, where one of the radicals R¹ and R² is always ≠ H, R¹ and R² together are alternatively alkylene having 3-5 carbon atoms,
- 15 R³ and R⁴ are each, independently of one another, H, A, OH, OA or Hal, R³ and R⁴ together are alternatively -O-CH₂-O-, X is R⁵ which is monosubstituted by R⁷,
- 20 R⁵ is linear or branched alkylene having 1-10 carbon atoms, or
 -C₆H₄-CH₂-,
- R⁷ is COOH or COOA,
- A is alkyl having from 1 to 6 carbon atoms,
- 25 Hal is F, Cl, Br or I,
- m is 1, and
- n is 1 or 2.
- 30 37. Pharmaceutical formulation according to Claim 31, comprising at least one compound of the formula I-II according to Claim 31, selected from the group consisting of
- (a) 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl]propionic acid;
- (b) 4-[4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl]butyric acid;
- 35

- (c) 7-[4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl]heptanoic acid;
 - (d) 7-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl]heptanoic acid;
 - 5 (e) 5-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl]valeric acid;
 - (f) 5-[4-(3-chloro-4-methoxybenzylamino)-6-methylthieno[2,3-d]-pyrimidin-2-yl]valeric acid;
 - 10 (g) 4-[4-(3-chloro-4-methoxybenzylamino)-6-methylthieno[2,3-d]-pyrimidin-2-yl]butyric acid;
 - (h) 4-[4-(3,4-methylenedioxybenzylamino)-6-methylthieno[2,3-d]-pyrimidin-2-yl]butyric acid;
 - (i) 2-[4-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno[2,3-d]pyrimidin-2-yl]cyclohexyl-1-yl]acetic acid;
 - 15 (k) 5-[4-(3,4-methylenedioxybenzylamino)-6-methylthieno[2,3-d]-pyrimidin-2-yl]valeric acid.
38. Pharmaceutical formulation according to Claim 31, comprising 5-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]pyrimidin-2-yl]valeric acid, ethanolamine salt.
- 20
39. Pharmaceutical formulation according to Claims 31 to 38, in which the endothelin receptor antagonist is selected from the group consisting of bosentan, tezosentan and sitaxentan.
- 25
40. Pharmaceutical formulation according to Claims 31 to 38, in which the endothelin receptor antagonist is selected from the group consisting of
- a) BMS-193884 (EP 558258),
 - b) BMS-207940 (Pharmaprojects (13.06.97)),
 - c) BQ-123 (Exp.Opin.Invest.Drugs, 1997, 6, No.5, 475-487),
 - d) SB-209670 (Exp.Opin.Invest.Drugs, 1997, 6, No.5, 475-487),
 - e) SB-217242 (Exp.Opin.Invest.Drugs, 1997, 6, No.5, 475-487),
 - f) SB-209598 (Trends in Pharmacol. Sci., 17, 177-81, 1996),
 - 30 g) TAK-044 (Exp.Opin.Invest.Drugs, 1997, 6, No.5, 475-487),
 - h) Bosentan (Trends in Pharmacol. Sci., 18, 408-12, 1997),

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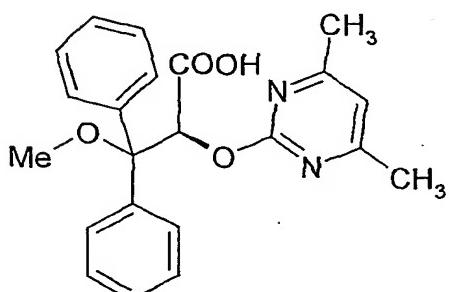
- i) PD-156707 (J.Med.Chem., 40, No.7, 1063-74, 1997),
- j) L-749329 (Bioorg.Med.Chem.Lett., 7, No.3, 275-280, 1997),
- k) L-754142 (Exp.Opin.Invest.Drugs, 1997, 6, No.5, 475-487),
- l) ABT-627 (J.Med.Chem., 40, No.20, 3217-27, 1997),
- 5 m) A-127772 (J.Med.Chem., 39, No.5, 1039-1048, 1996),
- n) A-206377 (213th American Chemical Society National Meeting, San Francisco, California, USA, 13 – 17 April 1997, Poster, MEDI 193),
- 10 o) A-182086 (J.Med.Chem., 40, No.20, 3217-27, 1997),
- p) EMD-93246 (211th American Chemical Society National Meeting, New Orleans, USA, 1996, Poster, MEDI 143),
- q) EMD-122801 (Bioorg.Med.Chem.Lett., 8, No.1, 17-22, 1998),
- r) ZD-1611 (Trends in Pharmacol. Sci., 18, 408-12, 1997),
- s) AC-610612 (R&D Focus Drug News (18.05.98)),
- 15 t) T-0201 (70th Annual Meeting of the Japanese Pharmacological Society, Chiba, Japan, 22-15 March 1997, Lecture, O-133),
- u) J-104132 (R&D Focus Drug News (15.12.97)),

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v)

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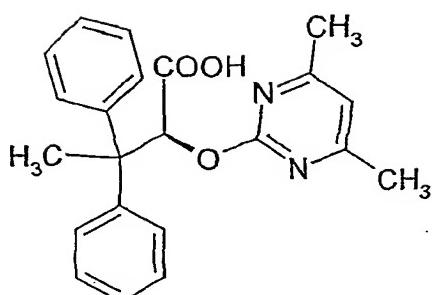
w)

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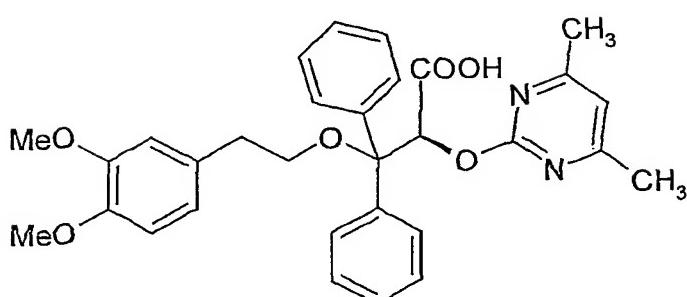
x)



10

y)

15

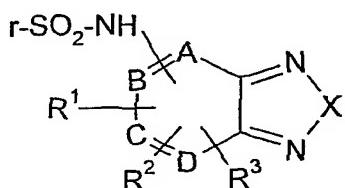


41. Pharmaceutical formulation according to Claims 31 to 38, in which
the endothelin receptor antagonist is selected from

20

a) the compounds of the formula I described in EP 0733626

25



I

in which

30

-A=B-C=D- is a -CH=CH-CH=CH- group in which 1 or 2 CH has
(have) been replaced by N,

Ar is Ph or naphthyl, each of which is unsubstituted or
monosubstituted, disubstituted or trisubstituted by H,
Hal, A, alkenyl having up to 6 carbon atoms, Ph, OPh,
NO₂, NR⁴R⁵, NHCOR⁴, CF₃, OCF₃, CN, OR⁴, COOR⁴,
(CH₂)_nCOOR⁴, (CH₂)_nNR⁴R⁵, -N=C=O or NHCONR⁴R⁵,

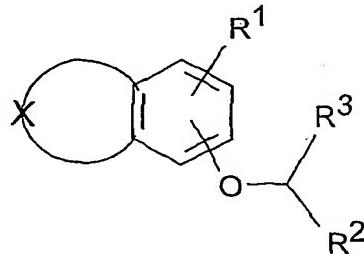
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R¹, R²
 and R³ are each, independently of one another, absent, H, Hal,
 A, CF₃, NO₂, NR⁴R⁵, CN, COOR⁴, NHCOR⁴,
 R⁴ and R⁵ are each, independently of one another, H or A, or
 5 together are alternatively -CH₂-(CH₂)_n-CH₂-,
 A is alkyl having from 1 to 6 carbon atoms,
 Ph is phenyl,
 X is O or S,
 Hal is F, Cl, Br or I,
 10 n is 1, 2 or 3,
 and their salts, with the exception of
 4-methyl-N-(2,1,3-benzothiadiazol-4-yl)benzenesulfonamide,
 4-methyl-N-(2,1,3-benzothiadiazol-5-yl)benzenesulfonamide, 4-nitro-
 N-(2,1,3-benzothiadiazol-4-yl)benzenesulfonamide, 4-nitro-N-(2,1,3-
 15 benzothiadiazol-5-yl)benzenesulfonamide, 4-amino-N-(2,1,3-benzo-
 thiadiazol-4-yl)benzenesulfonamide and 4-amino-N-(2,1,3-benzothia-
 diazol-5-yl)benzenesulfonamide;
 b) the compounds of the formula I described in EP 0733626

20

25



in which

30

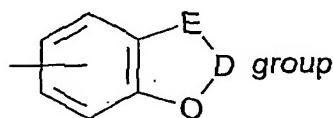
X is a saturated, partially unsaturated or completely unsaturated 3- to 4-membered alkylene chain, in which from 1 to 3 carbon atoms may be replaced by N and/or from 1 to 2 carbon atoms may be replaced by 1-2 O atoms and/or 1-2 S atoms, but where at most up to 3 carbon atoms may be replaced and where, in addition, a single, double or triple substitution of the alkylene chain

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and/or of a nitrogen located therein by A, R⁸ and/or NR⁴R^{4'} may occur, and where furthermore one CH₂ group in the alkylene chain may also be replaced by a C=O group,

- 5 A is alkyl having 1-6 carbon atoms, in which one or two CH₂ groups may be replaced by O or S atoms or by -CR⁴=CR^{4'}- groups and in addition 1-7 H atoms may be replaced by F,
- 10 R¹ is H or A,
- R² is COOR⁴, CN, 1H-tetrazol-5-yl or CONHSO₂R⁸,
- R³ is Ar,
- R⁴ and R^{4'} are each, independently of one another, H, alkyl having from 1 to 6 carbon atoms or benzyl,
- 15 Ar is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R⁵, R⁶ or R⁷, or is a



20

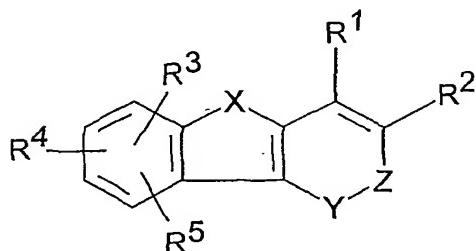
which is unsubstituted or monosubstituted or disubstituted in the phenyl part by R⁵ or R⁶,

- 25 R⁵, R⁶
 and R⁷ are each, independently of one another, R⁴, OR⁴, Hal, CF₃, OCF₃, OCH₂F, OCH₂F, NO₂, NR⁴R^{4'}, NHCOR⁴, CN, NHSO₂R⁴, COOR⁴, COR⁴, CONHSO₂R⁸, O(CH₂)_nR², OPh, O(CH₂)_nOR⁴ or S(O)_mR⁴,
- 30 R⁸ is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR¹, NR⁴R^{4'} or Hal,
- E is CH₂ or O,
- D is carbonyl or [C(R⁴R^{4')}]_n,
- Hal is F, Cl, Br or I,
- 35 m is 0, 1 or 2,
- n is 1 or 2,

and their salts;

c) the compounds of the formula I described in EP 0755934

5



10

in which

-Y-Z- is $-\text{NR}^7\text{-CO-}$, $-\text{N}=\text{C}(\text{OR}^7)\text{-}$ or $-\text{N}=\text{CR}^8\text{-}$,

R¹ is Ar,

R² is COOR^6 , CN, 1H-tetrazol-5-yl or CONHSO_2Ar ,

R³, R⁴ and R⁵ are each, independently of one another, R⁶, OR⁶, $\text{S(O)}_m\text{R}^6$, Hal, NO₂, NR⁶R⁶, NHCOR⁶, NHSO_2R^6 , OCOR⁶, COOR⁶ or CN,

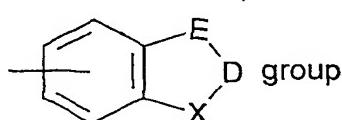
20 R⁶ and R^{6'} are each, independently of one another, H, alkyl having from 1 to 6 carbon atoms, benzyl or phenyl,

R⁷ is $(\text{CH}_2)_n\text{Ar}$,

R⁸ is Ar or OAr,

25 Ar is phenyl which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R⁹, R¹⁰ or R¹¹, or is unsubstituted naphthyl or a

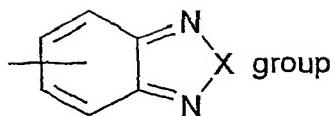
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which is unsubstituted or monosubstituted or disubstituted in the phenyl part by R⁹ or R¹⁰, or is a

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which is unsubstituted or monosubstituted or disubstituted in the cyclohexadienyl part by R⁹ or R¹⁰,

R⁹, R¹⁰

and R¹¹

are each, independently of one another, R⁶, OR⁶, Hal, CF₃, OCF₃, OCHF₂, OCH₂F, NO₂, NR⁶R⁶, NHCOR⁶, CN, NHSO₂R⁶, COOR⁶, COR⁶, CONHSO₂Ar, O(CH₂)_nR², O(CH₂)_nOR⁶ or S(O)_mR⁶,

10

E is CH₂, S or O,

D is carbonyl or [C(R⁶R⁶)]_n,

Hal is F, Cl, Br or I,

15

X is O or S,

m is 0, 1 or 2,

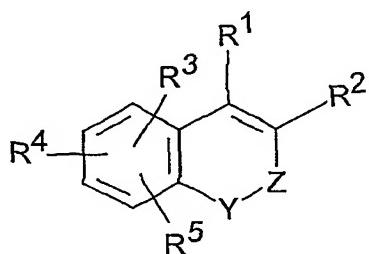
n is 1 or 2,

and their salts;

20

d) the compounds of the formula I described in EP 0757039

25



in which

-Y-Z- is -NR⁷-CO-, -N=C(OR⁷)- or -N=CR⁸-,

30

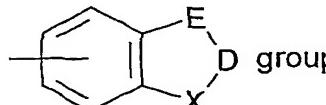
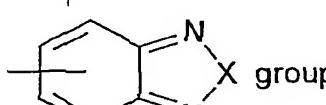
R¹ is Ar,

R² is COOR⁶, (CH₂)_nCOOR⁶, CN, 1H-tetrazol-5-yl or CONHSO₂Ar,

R³, R⁴

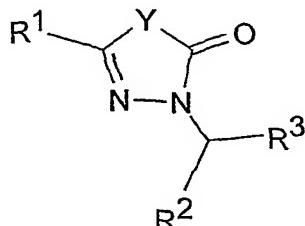
and R⁵ are each, independently of one another, R⁶, OR⁶, S(O)_mR⁶, Hal, NO₂, NR⁶R⁶, NHCOR⁶, NHSO₂R⁶,

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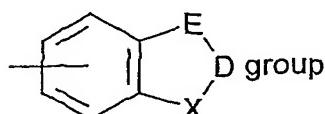
- OCOR⁶, COR⁶, COOR⁶ or CN, where R³ and R⁴ together may alternatively be an O(CH₂)_nO group, are each, independently of one another, H, alkyl having from 1 to 6 carbon atoms, benzyl or phenyl,
- 5 R⁶ and R^{6'} is (CH₂)_nAr,
 R⁸ is Ar or OAr,
 Ar is phenyl which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R⁹, R¹⁰ or R¹¹, or is unsubstituted naphthyl or a
- 10
- 
- 15
- which is unsubstituted or monosubstituted or disubstituted in the phenyl part by R⁹ or R¹⁰, or is a
- 20
- 
- which is unsubstituted or monosubstituted or disubstituted in the cyclohexadienyl part by R⁹ or R¹⁰,
- 25 R⁹, R¹⁰
 and R¹¹ are each, independently of one another, R⁶, OR⁶, Hal, CF₃, OCF₃, OCHF₂, OCH₂F, NO₂, NR⁶R^{6'}, NHCOR⁶, CN, NHSO₂R⁶, COOR⁶, COR⁶, CONHSO₂Ar, O(CH₂)_nR², O(CH₂)_nOR⁶ or S(O)_mR⁶,
- 30 E is CH₂, S or O,
 D is carbonyl or [C(R⁶R^{6'})]_n,
 X is O or S,
 Hal is F, Cl, Br or I,
 m is 0, 1 or 2,
 n is 1 or 2,
 and their salts;
- 35

- 175 -

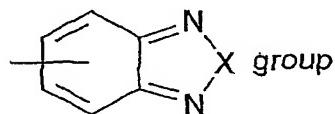
e) the compounds of the formula I described in EP 0796250



in which

10 Y is $-C(R^4R^4)-C(R^4R^4)-$, $-CR^4=CR^4-$ or $-C(R^4R^4)-S-$,R¹ is Het, Ar, R³ or R⁴,R² is Ar or a

which is unsubstituted or monosubstituted or disubsti-
20 tuted in the phenyl part by A, R³, OR⁴, NH₂, NHA, NA₂,
NO₂, CN, Hal, NHCOR⁴, NSO₂R⁴, COOR⁴, COR⁴,
CONHSO₂R⁶, O(CH₂)_nR³, OPh, O(CH₂)_nOR⁴ or S(O)_mR⁴,
or a



which is unsubstituted or monosubstituted or disubsti-
30 tuted in the cyclohexadienyl part by A, R³, OR⁴, NH₂,
NHA, NA₂, NO₂, CN, Hal, NHCOR⁴, NSO₂R⁴, COOR⁴,
COR⁴, CONHSO₂R⁶, O(CH₂)_nR³, OPh, O(CH₂)_nOR⁴ or
S(O)_mR⁴,

R³ is CN, COOH, COOA, CONHSO₂R⁵ or 1H-tetrazol-5-yl,

35

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	R^4 and R^4'	are each, independently of one another, H, A, or phenyl or benzyl, each of which is unsubstituted or monosubstituted by alkoxy,
5	R^5	is A or Ar,
	R^6	is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR ⁵ , NH ₂ , NHA, NA ₂ , NO ₂ , CN or Hal,
10	A	is alkyl having 1-6 carbon atoms, in which one or two CH ₂ groups may be replaced by O or S atoms or by -CR ⁴ =CR ^{4'} - groups and in addition 1-7 H atoms may be replaced by F,
		or benzyl,
	Ar	is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR ⁴ , NH ₂ , NHA, NA ₂ , NO ₂ , CN, Hal, NHCOR ⁴ ,
15		NHSO ₂ R ⁴ , COOR ⁴ , COR ⁴ , CONHSO ₂ R ⁶ , O(CH ₂) _n R ³ , OPh, O(CH ₂) _n OR ⁴ or S(O) _m R ⁴ ,
	Het	is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/or S atoms, bonded via N or C, which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, R ³ , NH ₂ , NHA, NA ₂ , CN, NO ₂ and/or carbonyl oxygen,
20	D	is carbonyl or [C(R ⁴ R ^{4'})] _n ,
25	E	is CH ₂ , S or O,
	Hal	is F, Cl, Br or I,
	X	is O or S,
	m	is 0, 1 or 2,
	n	is 1 or 2,
30		and their salts;

f) the compounds of the formula I described in WO 9719077

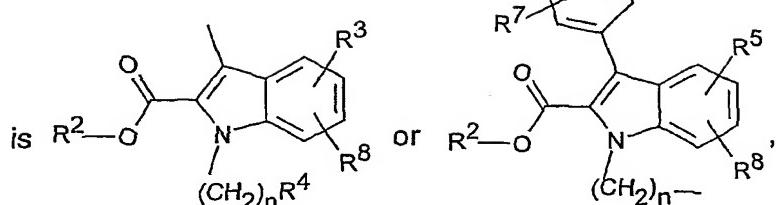
- 177 -



in which

10

R



15

X is O or S,

R¹ is H, Hal, OH, OA, A, alkylene-O-A, NO₂, NH₂, NH-acyl, SO₂NH₂, SO₃-A, SO₂NHA, CN or formyl,R² is H or A,R³, R⁵, R⁶20 R⁷ and R⁸ are each, independently of one another, H, Hal, OH, OA, O-alkylene-R⁴, A, S-A, NO₂, NH₂, NHA, NA₂, NH-acyl, NHSO₂A, NHSO₂R⁴, NASO₂A, NASO₂-R⁴, NH(CO)NH₂, NH(CO)NHA, formyl, NH(CO)NH-phenyl, NHCOOA, NA-acyl, NHR⁴, NHCOOR⁴, NHCOO-benzyl, NHSO₂-benzyl, NHCOO-alkylene-OA, NH(CO)NA₂, N-piperidinyl-CO-NH, N-pyrrolidinyl-CONH, O(CH₂)_nCOOR², O(CH₂)_nOR², CH₂OH or CH₂OA,25 R³ and R⁶ together are alternatively -O-CH₂-O-, -O-CH₂-CH₂-O-, -O-CH₂-CH₂-O- or -O-CF₂-O- or -O-CF₂-CF₂-O-,30 R⁴ is phenyl which is unsubstituted or monosubstituted or polysubstituted by R³ and/or R⁶,

A is alkyl having 1-6 carbon atoms,

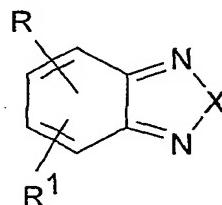
Hal is fluorine, chlorine, bromine or iodine,

n is 1 or 2,

35 and their salts;

g) the compounds of the formula I described in WO 9730982

5

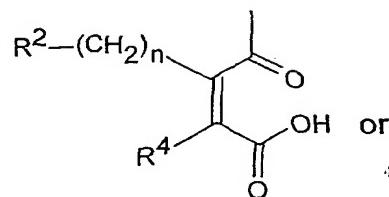
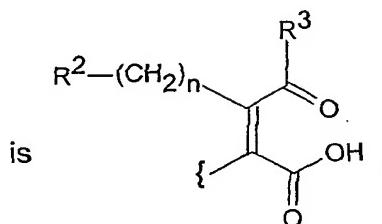


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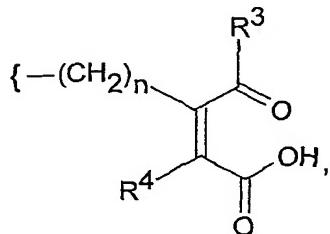
10

in which

R



15



20

X

is O or S,

R¹

is H, Hal, OH, OA, A, alkylene-O-A, NO₂, NH₂, NH-acyl, SO₂NH₂, SO₃-A, SO₂NHA, CN or formyl,

R², R³

and R⁴ are each, independently of one another, a phenyl group

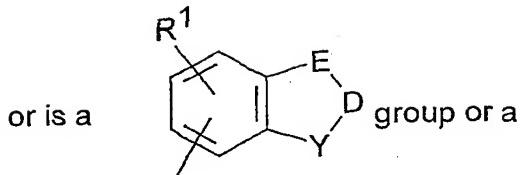
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which is unsubstituted or monosubstituted or polysubstituted by Hal, OH, OA, O-alkylene-R⁵, A, S-A, SOA, SO₂A, SOR⁵, SO₂R⁵, NO₂, NH₂, NHA, NA₂, NH-acyl, NHSO₂A, NHSO₂R⁵, NASO₂A, NASO₂-R⁵, NH(CO)NH₂, NH(CO)NHA, formyl, NH(CO)NHR⁵, NHCOOA, NA-acyl, NHCOOCH₂R⁵, NHSO₂CH₂R⁵, NHCOO-alkylene-OA, NH(CO)NA₂, 1-piperidinyl-CO-NH, 1-pyrrolidinyl-CONH, O(CH₂)ₙCOOA, O(CH₂)ₙCOOH, O(CH₂)ₙOH, O(CH₂)ₙOA, CH₂OH, CH₂OA, COOH, COOA, CH₂COOH or CH₂COOA,

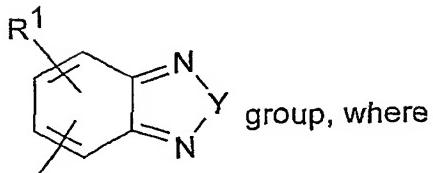
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R^5 R^2 is additionally A or cycloalkyl,
is a phenyl group which is unsubstituted or monosubsti-
tuted or polysubstituted by Hal, OH, OA, A, S-A, NO₂,
NH₂, NHA, NA₂, NH-acyl, NHSO₂A, NASO₂A,
NH(CO)NH₂, NH(CO)NHA, formyl, NHCOOA, NA-acyl,
NHCOO-alkylene-OA, NH(CO)NA₂, N-piperidinyl-CO-
NH, N-pyrrolidinyl-CONH, O(CH₂)_nCOOA,
O(CH₂)_nCOOH, O(CH₂)_nOH, O(CH₂)_nOA, CH₂OH,
CH₂OA, COOH, COOA, CH₂COOH or CH₂COOA.

15

A is alkyl having 1-6 carbon atoms, in which one or two
CH₂ groups may be replaced by O or S atoms or by
-CR⁶=CR⁶- groups and/or 1-7 H atoms may be replaced
by F,

20

D is carbonyl or [C(R⁶R⁶)]_m,

E is CH₂, S or O,

25

Y is O or S,

R^6 and $R^{6'}$ are each, independently of one another, H, F or A,

Hal is fluorine, chlorine, bromine or iodine,

n is 1 or 2, and

m is 1 or 2,

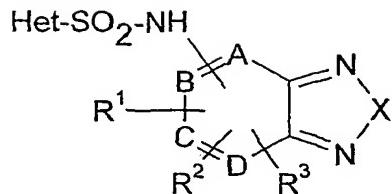
30

or a tautomeric cyclised form, and the (E)-isomers and the salts of all
isomers;

h) the compounds of the formula I described in WO 9730996

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5

in which

-A=B-C=D- is a -CH=CH-CH=CH- group, in which, in addition, 1 or 2 CH may be replaced by N,

10

Het is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/or S atoms which is unsubstituted or substituted by -Z-R⁶,

15

R¹, R² and R³ are each, independently of one another, absent, H, Hal, A, CF₃, NO₂, NR⁴R⁵, CN, COOR⁴ or NHCOR⁴,

R⁴ and R⁵ are each, independently of one another, H or A, or together are alternatively -CH₂-(CH₂)_n-CH₂-,

20

R⁶ is a phenyl radical, benzothiadiazol-5-yl or benzoxadiazol-5-yl radical, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R⁷, R⁸ and/or R⁹,

25

R⁷, R⁸ and R⁹ are each, independently of one another, A, O-A, CN, COOH, COOA, Hal, formyl, -CO-A, and R⁷ and R⁸ are alternatively -O-(CH₂)_m-O-,

A is alkyl having from 1 to 6 carbon atoms,
X is O or S,
Z is -CO-, -CONH-, -CO-(CH₂)_n-, -CH=CH-, -(CH₂)_n-, -CONHCO-, -NHCONH-, -NHCOO-, -O-CONH-, -CO-O- or -O-CO-,

30

Hal is F, Cl, Br or I,

m is 1 or 2, and

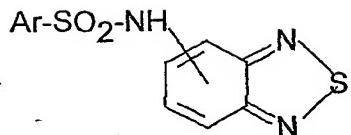
n is 1, 2 or 3,

and their salts;

35

i) the compounds of the formula I described in DE 1960957

- 181 -



5

in which

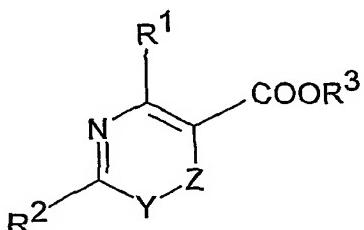
Ar is naphthyl which is monosubstituted by NH₂, NHA or
NA₂, and

10

A is alkyl having from 1 to 6 carbon atoms,
and their physiologically acceptable salts;

j) the compounds of the formula I described in DE 19612101

-15



20

in which

-Y-Z- is -NR⁴-CO or -N=CR⁵-,

R¹ is Ar,

R² is H, alkyl having 1-6 carbon atoms which is unsubstituted or monosubstituted, disubstituted or trisubstituted by OR³ or Hal, or (CH₂)_mPh or (CH₂)_m-cycloalkyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R³, OR³ or Hal,

25

R³ and R^{3'} are each, independently of one another, H, alkyl having 1-6 carbon atoms or benzyl,

30

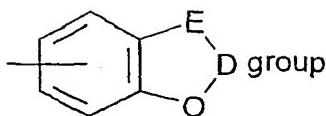
R⁴ is CH₂Ar,

R⁵ is OCH₂Ar,

Ar is phenyl which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R⁶, R⁷ or R⁸, or a

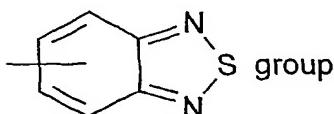
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which is unsubstituted or monosubstituted in the phenyl part by R⁶, or a



10

which is unsubstituted or monosubstituted in the cyclohexadienyl part by R⁶,

E is CH₂ or O,

D is carbonyl or (CH₂)_n,

15

E and D together are alternatively CH=CR⁹,

R⁶, R⁶' are each, independently of one another, R³, OR³ or Hal,

R⁷ is R³, OR³, Hal, NO₂, NH₂, NHR³, NR³R³', NHCOR³, COOR³, O(CH₂)_nR³ or O(CH₂)_nOR³,

R⁸ is Ph which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R³, OR³, Hal, NO₂, NH₂, NHR⁶, NR⁶R⁶', NHCOR³ or COOR³,

20

R⁹ is H, OH, CH₂OH or COOR³,

Hal is F, Cl, Br or I,

Ph is phenyl,

25

m is 0 or 1,

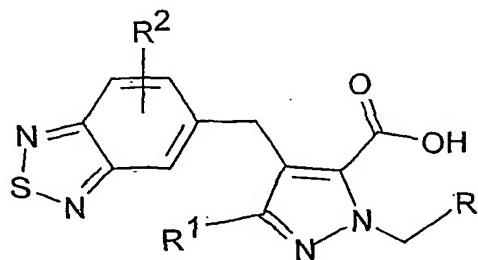
n is 1 or 2,

and their salts;

30

k) the compounds of the formula I described in WO 9827091

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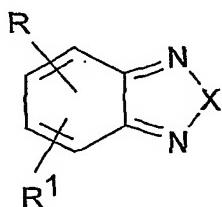
- 183 -

in which

- 5 R is phenyl which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R³, R⁴ or R⁵, or 2,1,3-benzothiadiazolyl which is unsubstituted or mono-substituted by R²,
- 10 R¹ is A, in which 1-7 H atoms may be replaced by F, is -S-A, -O-A, is phenyl or -alkylene-phenyl, each of which is unsubstituted or monosubstituted by R³, or is thiienyl which is unsubstituted or monosubstituted by R³,
- 15 R² is A, F, Cl, Br or -O-A,
- R³, R⁴
and R⁵ are each, independently of one another, A, -O-A, -S-A, -O-alkylene-COOH, -alkylene-COOH or COOH,
- R³ and R⁴ together are alternatively -O-CH₂-O-, and
- 20 A is alkyl having 1-7 carbon atoms,
and their salts;

I) the compounds of the formula I described in WO 9827077

20



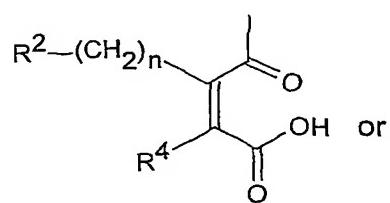
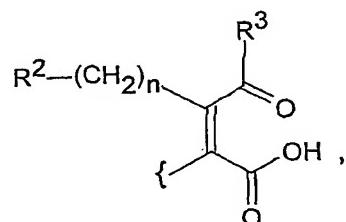
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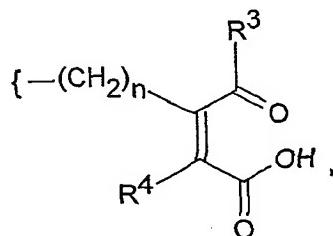
in which

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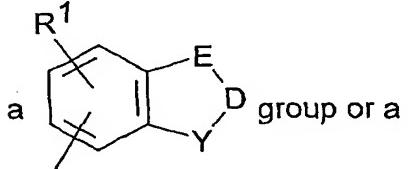
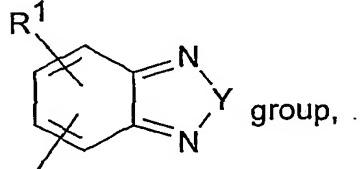
R is



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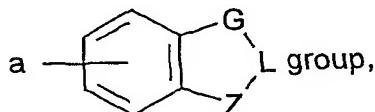
- 184 -

- X is O or S,
 R¹ is H, Hal, OH, OA, A, alkylene-O-A, NO₂, NH₂, NH-acyl, SO₂NH₂, SO₃-A, SO₂NHA, CN or formyl,
- 5 R², R³ and R⁴ are each, independently of one another, a phenyl group which is unsubstituted or monosubstituted or polysubstituted by R⁷, where R² is additionally A or cycloalkyl, or are
- 10 
- 15 
- 20 with the proviso that at least one of the radicals R², R³ or R⁴ is an R⁸ radical which is unsubstituted or mono-substituted or polysubstituted by R⁷,
- R⁵ is a phenyl group which is unsubstituted or monosubstituted or polysubstituted by Hal, OH, OA, A, S-A, NO₂, NH₂, NHA, NA₂, NH-acyl, NSO₂A, NASO₂A, NH(CO)NH₂, NH(CO)NHA, formyl, NHCOOA, NA-acyl, NHCOO-alkylene-OA, NH(CO)NA₂, N-piperidinyl-CO-NH, N-pyrrolidinyl-CONH, O(CH₂)_nCOOA, O(CH₂)_nCOOH, O(CH₂)_nOH, O(CH₂)_nOA, CH₂OH, CH₂OA, COOH, COOA, CH₂COOH or CH₂COOA,
- 25 A is alkyl having 1-6 carbon atoms, in which one or two CH₂ groups may be replaced by O or S atoms or by -CR⁶=CR⁶- groups and/or 1-7 H atoms may be replaced by F,
- 30 D is carbonyl or [C(R⁶R⁶)]_m,
 E is CH₂, S or O,
- 35

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- Y is O or S,
 R⁶ and R^{6'} are each, independently of one another, H, F or A,
 R⁷ is Hal, OH, OA, O-alkylene-R⁵, A, S-A, S-OA, SO₂A,
 5 S-OR⁵, SO₂R⁵, NO₂, NH₂, NHA, NA₂, NH-acyl, NSO₂A,
 NHSO₂R⁵, NASO₂A, NASO₂-R⁵, NH(CO)NH₂,
 NH(CO)NHA, formyl, NH(CO)NHR⁵, NHCOOA, NA-acyl,
 NHCOOCH₂R⁵, NSO₂CH₂R⁵, NHCOO-alkylene-OA,
 NH(CO)NA₂, 1-piperidinyl-CO-NH, 1-pyrrolidinyl-CONH,
 O(CH₂)_nCOOA, O(CH₂)_nCOOH, O(CH₂)_nOH, O(CH₂)_nOA,
 10 CH₂OH, CH₂OA, COOH, COOA, CH₂COOH or
 CH₂COOA,
 R⁸ is a 5-7-membered heterocyclic radical having 1-4 N, O
 and/or S atoms or is

15



20

20

- G and Z are each, independently of one another, -CH=, N, O or
 S,

L is -CH=, -CH=CH- or -CH₂-CH₂-CH₂-,

Hal is fluorine, chlorine, bromine or iodine,

n is 0, 1 or 2, and

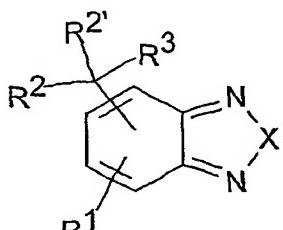
m is 1 or 2,

25

- or a tautomeric cyclised form, and the (E)-isomers and the salts of all
 isomers;

m) the compounds of the formula I described in WO 9841515

30



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in which

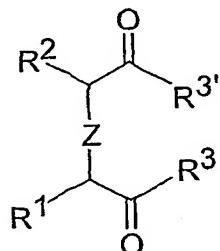
X	is O or S,
R ¹	is H, Hal, OH, OA, A, NO ₂ , NH ₂ , NHA, NAA', NHCOR ⁴ , NHCOR ⁶ , NHSO ₂ R ⁴ , NHSO ₂ R ⁶ , S(O) _m R ⁶ , SO ₃ H, SO ₂ NR ⁴ R ⁴ or formyl,
5 R ² and R ^{2'}	are each, independently of one another, A, (CH ₂) _n Ar, (CH ₂) _n Het, CH ₂ COAr, CH ₂ COHet or OAr,
R ^{2'}	is additionally also H,
R ³	is COOR ⁴ , CN, 1H-tetrazol-5-yl or CONHSO ₂ R ⁵ ,
10 R ⁴ and R ^{4'}	are each, independently of one another, H or A,
R ⁵	is A or Ar,
R ⁶	is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, NH ₂ , NHA, NAA', NO ₂ , CN or Hal,
15 R ⁷ and R ^{7'}	are each, independently of one another, H or alkyl having 1-6 carbon atoms,
A and A'	are each, independently of one another, alkyl having 1-6 carbon atoms, in which one or two CH ₂ groups may be replaced by O or S atoms or by -CR ⁷ =CR ^{7'} - groups and/or 1-7 H atoms may be replaced by F, or benzyl,
20 Ar	is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR ⁴ , NH ₂ , NHA, NAA', NO ₂ , CN, Hal, NHCOR ⁴ , NHCOR ⁶ , NHSO ₂ R ⁴ , NHSO ₂ R ⁶ , COOR ⁴ , OPh, CONH ₂ , CONHA, CONAA', COR ⁴ , CONHSO ₂ R ⁴ , CONHSO ₂ R ⁶ , O(CH ₂) _n COOR ⁴ , O(CH ₂) _n OR ⁴ , SO ₃ H, SO ₂ NR ⁴ R ⁴ , S(O) _m R ⁶ or S(O) _m R ⁴ ,
25 Het	is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having 1-4 N, O and/or S atoms, bonded via N or C, which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, R ³ , NH ₂ , NHA, NAA', NO ₂ and/or =O,
30 Hal	is fluorine, chlorine, bromine or iodine,
35 m	is 0, 1 or 2, and
n	is 1 or 2,

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where, if R^2 is CH_2COAr and R^2 is H, R^3 is not $COOA$,
and salts thereof;

n) the compounds of the formula I described in WO 9841521

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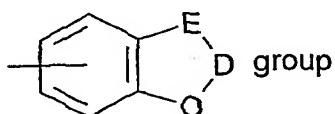
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in which

Z is a single or double bond,

R¹ is a

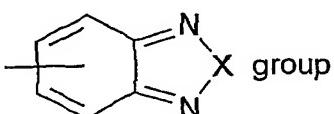
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20

which is unsubstituted or monosubstituted in the phenyl part by R⁷, or is a

25



which is unsubstituted or monosubstituted in the cyclohexadienyl part by R⁷,

30

R² is A, Ar-(CH₂)_m, cycloalkyl-(CH₂)_m, Het-(CH₂)_m or R¹-(CH₂)_m,

R³ and R^{3'} are each, independently of one another, OR⁴, NSO₂R⁵, NH₂, NHA or NAA',

R³ and R^{3'} together are alternatively -O-, forming a cyclic anhydride,

R⁴ and R^{4'} are each, independently of one another, H or A,

R⁵ is A or Ar,

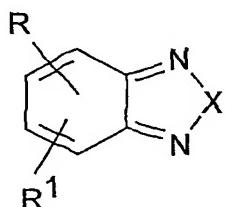
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R⁶ is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, NH₂, NHA, NAA', NO₂, CN or Hal,
 5 R⁷ is A, COOR⁴, CN, 1H-tetrazol-5-yl, CONHSO₂R⁵, Hal, OR⁴, NO₂, NH₂, NHA, NAA', NHCOR⁴, NHCOR⁶, NHSO₂R⁴, NHSO₂R⁶, S(O)_kR⁴, S(O)_kR⁶, SO₂NR⁴R⁴ or formyl,
 R⁸ and R^{8'} are each, independently of one another, H or alkyl having 1-6 carbon atoms,
 10 E is CH₂ or O,
 D is carbonyl or (CR⁴R⁴)_n,
 E and D together are alternatively CR⁴=R⁴,
 X is S or O,
 A and A' are each, independently of one another, alkyl having 1-6 carbon atoms, in which one or two CH₂ groups may be replaced by O or S atoms or by -CR⁸=CR^{8'}- groups and/or 1-7 H atoms may be replaced by F, or benzyl,
 15 Ar is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR⁴, NH₂, NHA, NAA', NO₂, CN, Hal, NHCOR⁴, NHCOR⁶, NHSO₂R⁴, NHSO₂R⁶, COOR⁴, OPh, CONH₂, CONHA, CONAA', COR⁴, CONHSO₂R⁴, CONHSO₂R⁶, O(CH₂)_nCOOR⁴, O(CH₂)_nOR⁴, SO₂NR⁴R⁴, S(O)_kR⁶ or S(O)_kR⁴,
 20 Het is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having 1-4 N, O and/or S atoms, bonded via N or C, which may be unsubstituted, monosubstituted or disubstituted or trisubstituted by Hal, A, COOR⁴, CN, 1H-tetrazol-5-yl, CONHSO₂R⁵, NH₂, NHA, NAA', NO₂ and/or =O,
 25 Hal is fluorine, chlorine, bromine or iodine,
 k is 0, 1 or 2,
 m is 0, 1 or 2, and
 n is 1 or 2,
 30 and the (Z)- and (E)-isomers and the salts of all isomers;
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o) the compounds of the formula I described in WO 9842702

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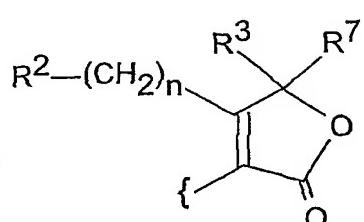


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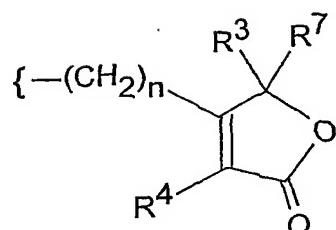
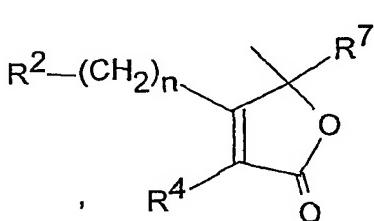
10

in which

R



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20

X and Y are each, independently of one another, O or S,

R¹ is H, Hal, OH, OA, A, alkylene-O-A, NO₂, NH₂, NH-acyl, SO₂NH₂, SO₂-A, SO₂NHA, CN or formyl,

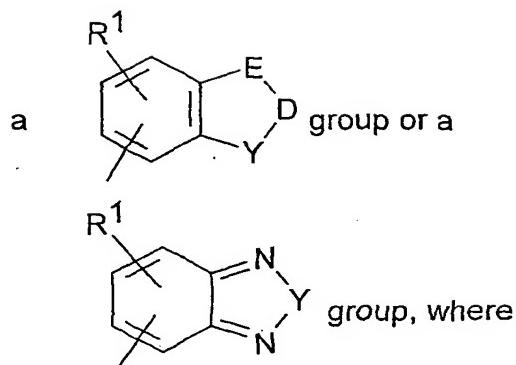
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R², R³ and R⁴ are each, independently of one another, a phenyl group which is unsubstituted or monosubstituted or polysubstituted by Hal, OH, OA, O-alkylene-R⁵, A, S-A, S-OA, SO₂A, S-OR⁵, SO₂R⁵, NO₂, NH₂, NHA, NA₂, NH-acyl, NHSO₂A, NHSO₂R⁵, NASO₂A, NASO₂-R⁵, NH(CO)NH₂, NH(CO)NHA, formyl, NH(CO)NHR⁵, NHCOOA, NA-acyl, NHCOOCH₂R⁵, NHSO₂CH₂R⁵, NHCOO-alkylene-OA, NH(CO)NA₂, 1-piperidinyl-CO-NH, 1-pyrrolidinyl-CONH, O(CH₂)_nCOOA, O(CH₂)_nCOOH, O(CH₂)_nOH, O(CH₂)_nOA, CH₂OH, CH₂OA, COOH, COOA, CH₂COOH or CH₂COOA,

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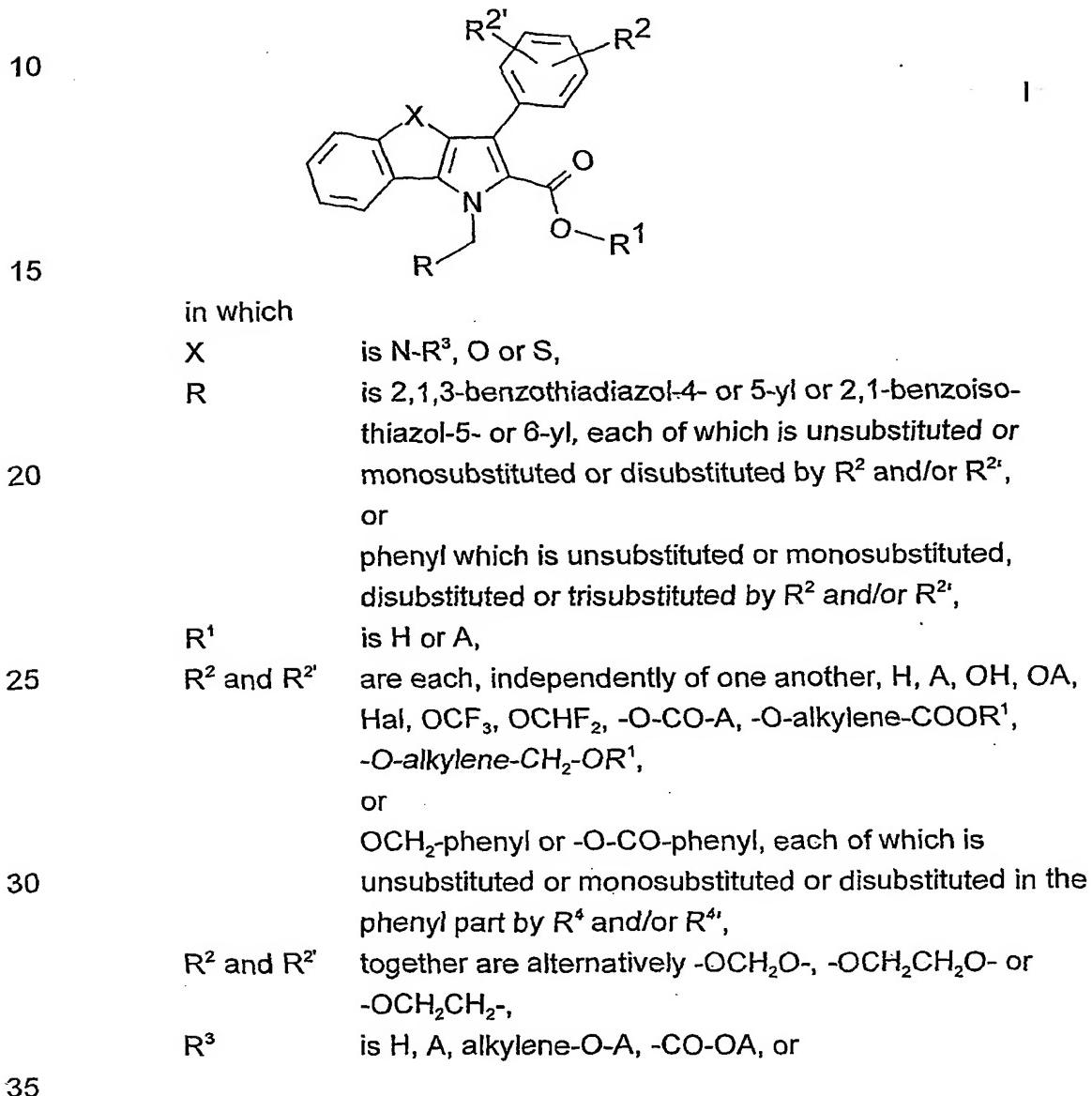
- 190 -



- 10 R^5 R^2 is additionally A or cycloalkyl,
is a phenyl group which is unsubstituted or monosubstituted
or polysubstituted by Hal, OH, OA, A, S-A, NO₂,
NH₂, NHA, NA₂, NH-acyl, NSO₂A, NASO₂A,
NH(CO)NH₂, NH(CO)NHA, formyl, NHCOOA, NA-acyl,
NHCOO-alkylene-OA, NH(CO)NA₂,
- 15 A N-piperidinyl-CO-NH, N-pyrrolidinyl-CONH,
 $O(CH_2)_nCOOA$, $O(CH_2)_nCOOH$, $O(CH_2)_nOH$, $O(CH_2)_nOA$,
CH₂OH, CH₂OA, COOH, COOA, CH₂COOH or
CH₂COOA,
- 20 A is alkyl having 1-6 carbon atoms, in which one or two
CH₂ groups may be replaced by O or S atoms or by
-CR⁶=CR⁶- groups and/or 1-7 H atoms may be replaced
by F,
- 25 D is carbonyl or [C(R⁶R⁶)]_m,
- E is CH₂, S or O,
- R⁶ and R⁶' are each, independently of one another, H, F or A,
- R⁷ is -O-C(=Y)-NH-R⁸,
- R⁸ is alkyl having 1-10 carbon atoms which is unsubstituted
or monosubstituted or disubstituted by R⁸ and in which
1-2 carbon atoms may be replaced by O and/or S,
and/or may be substituted by =O,
or
cycloalkyl, in which 1-2 carbon atoms may be replaced
by N, O and/or S,
- 30 R⁹ is phenyl which is unsubstituted or monosubstituted or
disubstituted by Hal,

or is naphthyl, A-O-C(=O)- or Hal,
 Hal is fluorine, chlorine, bromine or iodine,
 n is 0, 1 or 2, and
 m is 1 or 2,
 5 and salts thereof;

p) the compounds of the formula I described in WO 9842709

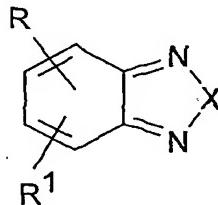


alkylene-phenyl which is unsubstituted or mono-substituted or disubstituted in the phenyl part by R⁴ and/or R⁴,

- 5 R⁴ and R⁴ are each, independently of one another, H, A, OH, OA, Hal, COOR¹ or CH₂OR¹,
A is alkyl having 1-6 carbon atoms,
Hal is fluorine, chlorine, bromine or iodine,
and their salts;

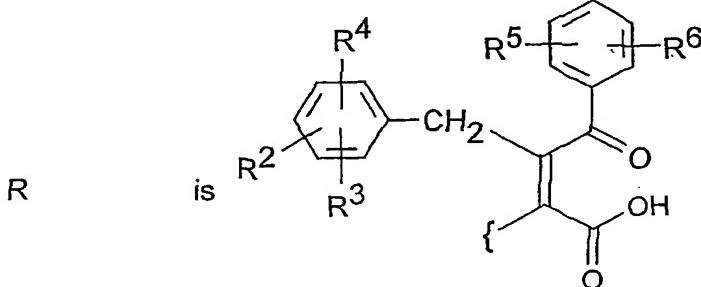
- 10 q) the compounds of the formula I described in WO 9905132

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in which

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- X is O or S,
R¹ is H, Hal, OA or A,
R², R³ R⁵,
30 and R⁶ are each, independently of one another, H, Hal, A, OA or R⁴,
R⁴ is -O-(CH₂)_n-Cy,
Cy is cycloalkyl having 3-8 carbon atoms,
A is alkyl having 1-6 carbon atoms, in which one or two
35 CH₂ groups may be replaced by O or S atoms or by

-CR⁵=CR⁵- groups and/or 1-7 H atoms may be replaced by F,

R⁵ and R^{5'} are each, independently of one another, H, F or A,

Hal is fluorine, chlorine, bromine or iodine,

5 n is 0, 1 or 2,

or a tautomeric cyclised form, and the (E)-isomers and the salts of all isomers.

- 10 42. Pharmaceutical formulation according to one of the preceding claims, comprising one or more excipients and/or assistants.
- 15 43. Use of a pharmaceutical preparation according to one of Claims 31 to 42 for the preparation of a medicament for the treatment of angina, high blood pressure, high pulmonary pressure, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cor pulmonale, dextrocardiac insufficiency, atherosclerosis, conditions of reduced patency of the heart vessels, peripheral vascular diseases, strokes, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, irritable bowel syndrome, tumours, renal insufficiency, liver cirrhosis, erectile dysfunction and for the treatment of female sexual disorders.
- 20 44. Use according to Claim 43 for the preparation of a medicament for the treatment of high pulmonary pressure, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cor pulmonale and/or dextrocardiac insufficiency.
- 25 45. Set (kit) consisting of separate packs of
(a) an effective amount of 5-[4-(3-chloro-4-methoxybenzyl-amino)-5,6,7,8-tetrahydro-[1]benzothieno[2,3-d]pyrimidin-2-yl]valeric acid and/or physiologically acceptable salts and/or solvates thereof and
(b) an effective amount of an endothelin receptor antagonist.

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(71) Applicant (for all designated States except US): **MERCK PATENT GMBH [DE/DE]**; Frankfurter Strasse 250, 64293 Darmstadt (DE).

(72) Inventors; and

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(74) Common Representative: **MERCK PATENT GMBH**; Frankfurter Strasse 250, 64293 Darmstadt (DE).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

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21 November 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

A3

WO 02/062343 A3

(54) Title: **PHARMACEUTICAL FORMULATION COMPRISING PYRAZOLO[4,3-d]PYRIMIDINES AND ENDOTHELIN RECEPTOR ANTAGONISTS OR THIENOPYRIMIDINES AND ENDOTHELIN RECEPTOR ANTAGONISTS**

(57) Abstract: Pharmaceutical preparation comprising at least one phosphodiesterase V inhibitor have, and/or physiologically acceptable salts and/or solvates thereof and at least one endothelin receptor antagonist for the preparation of a medicament for the treatment of angina, high blood pressure, high pulmonary pressure, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cor pulmonale, dextrocardiac insufficiency, atherosclerosis, conditions of reduced patency of the heart vessels, peripheral vascular diseases, strokes, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, irritable bowel syndrome, tumours, renal insufficiency, liver cirrhosis, erectile dysfunction and for the treatment of female sexual disorders.

INTERNATIONAL SEARCH REPORT

National Application No
PCT/EP 02/00256

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/505 A61K31/27 A61P25/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, EMBASE, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 64004 A (SQUIBB BRISTOL MYERS CO) 16 December 1999 (1999-12-16) cited in the application claims 1,17	1-15
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	---	-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

29 August 2002

05.09.2002

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Fax: (+31-70) 340-3016

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Beyss, E

INTERNATIONAL SEARCH REPORT

National Application No
PCT/EP 02/00256

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 037 346 A (DOHERTY JR PAUL C ET AL) 14 March 2000 (2000-03-14) claims 1,3,4 ---	1
A	US 6 174 884 B1 (NIEWOEHNERR ULRICH ET AL) 16 January 2001 (2001-01-16) claim 1 ---	1
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A	US 6 130 223 A (CHRISTADLER MARIA ET AL) 10 October 2000 (2000-10-10) claims 1,3 ---	16,31
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/00256

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-15

Pharmaceutical formulation comprising at least a phosphodiesterase V inhibitor of formula I and at least an endothelin receptor antagonist

2. Claims: 16-45

Pharmaceutical formulation comprising at least a phosphodiesterase V inhibitor of formula I-I or I-II and at least an endothelin receptor antagonist.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/00256

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INTERNATIONAL SEARCH REPORT

Information on patent family members

National Application No	
PCT/EP 02/00256	

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